

Clinical Communications

Vitamin A Tolerance Test and Fat Metabolism Disorders in Angina Pectoris

*Jean-Louis Beaumont, M.D., and Jean Lenègre, M.D., Paris, France.
With the Technical Assistance of M. Antonucci*

Angina pectoris is related in more than 95 per cent of the cases* to occlusive atherosclerosis of the coronary arteries,¹ thus allowing the selection of observations particularly favorable to the study of the metabolic disorder or disorders eventually responsible for atherogenesis.

The analysis of fasting blood lipids is the first step in this study, and provides to-day, with the help of ultracentrifugation and electrophoresis, an information more complete than that derived from a simple chemical analysis. But the modifications thus detected are still inconstant and polymorphic: inconstant, because at least 20 per cent of the patients have normal fasting blood lipids whatever the method of analysis used²⁻⁴; and polymorphic, because the common rise in serum cholesterol and β - or low-density lipoproteins masks qualitatively different changes in blood lipids, that is, the pattern of the lipoproteins involved⁴⁻⁶ and their sensitivity to heparin⁴ and to diet⁵ are not similar in all patients, thus suggesting the presence of different metabolic disorders. Moreover, the characteristics of one of the commonest patterns of high blood lipids suggests a disorder in the first stages of fat metabolism (absorption, transport, storage).⁴

The expression of such a disorder might be limited to the postabsorptive period and thus escape the mere dosage of fasting blood lipids. This justifies the performance of fat tolerance tests: a vitamin A tolerance test was used here, because it has many advantages over the conventional tests. The vitamin A ester behaves like a real tracer of neutral fat during the first stages of its me-

From the Department of Cardiology, Boucicaut Hospital, Paris, France.

Received for publication March 18, 1959.

*If angina pectoris associated with syphilitic aortitis, aortic stenosis, or major hypertension are excluded.

tabolism.^{7,8} The vitamin A tolerance test and the conventional fat tolerance tests usually yield parallel curves: they are low in steatorrheas,^{9,10} and high in essential hyperlipemia.^{7,11}

MATERIAL AND METHODS

The vitamin A tolerance test¹² was performed with a natural vitamin A ester in an oily medium. The test lasted 4 days: 100,000 units were given per os at 9 A.M. on the first and second days; nothing was given on the third day; and 500,000 units were given at 9 A.M. on the fourth day. Breakfast was taken immediately afterward, compulsorily consisting of coffee, milk, sugar, bread, and 15 grams of butter. Samples of blood for vitamin A assay were collected on the morning of the first day, before the 100,000 units were given, and again on the fourth day, just before the ingestion of the 500,000 units, and 3, 6, 9, and 24 hours afterward. In the last 46 patients an additional sample was collected 12 hours afterward.

Blood vitamin A was measured by the method of Embree, Ames, Lehmann and Harris,¹³ and the results were expressed in international units per 100 ml. of serum, using crystallized vitamin A as a standard. The normal limits of the vitamin A tolerance test were indicated by the results obtained in 19 cardiac patients,¹² ranging in age from 20 to 60 years, who were free of atherosclerotic disease and of any disease or treatment known to modify fat metabolism (Table I). These limits are similar to those already reported by others.^{10,14,15}

A total of 54 patients was studied*: 10 women and 44 men, ranging in age from 32 to 73 years—6 were 30 to 39, 15 were 40 to 49, 20 were 50 to 59, 9 were 60 to 69, and 4 were over 70 years.

All of the patients complained of angina pectoris (angina of effort) and were free of aortic stenosis, syphilitic aortitis, or major arterial hypertension. They were divided into six groups, according to clinical data and chemical and paper electrophoretic data of blood lipids in the fasting state. (1) Seven patients had primary hypercholesterolemia (ranging from 350 to 600 mg. per cent) with very high levels of a β -lipoprotein insensitive to heparin action *in vivo*.† Two of them had familial hypercholesterolemic xanthomatosis with tendon xanthoma, and five had exactly the same picture without any tendon xanthoma. (2) Eight patients had primary or essential hyperlipemia (total lipids ranging from 1,400 to 3,000 mg. per cent) with high levels of neutral fat and of a lipoprotein very sensitive to heparin action *in vivo*† (probably chylomicra). The fasting serum was intensely milky in 2, and only slightly so in the 6 others. (3) Two patients had hyperlipemia of diabetic origin (untreated). (4) One patient had hypercholesterolemia of myxedematous origin (untreated). (5) Twenty-four patients had an atypical and usually moderate increase of blood lipids which could not be fitted into any of the preceding patterns. However, 14 of them had a relative increase in pre and post β -lipoproteins very sensitive to heparin.† (6) Twelve patients had normal fasting blood lipids.

RESULTS

In the 54 patients with angina pectoris the vitamin A tolerance test gave mean results differing from the normal in four different points: the starting level was higher, the peak delayed and higher, and the return to the base level delayed also (Table II).

But the curves taken individually were within normal limits in 26 cases, above normal in 23, and below normal in 5. These divergent findings when correlated with the six groups differentiated according to clinical and fasting

*Fifteen additional cases were added to the 39 already studied in a previous report.¹⁶

†The sensitivity of lipoproteins to heparin is judged by comparing the paper electrophoretic pattern of lipids before and after an intravenous injection of heparin, 25 mg. When heparin-sensitive lipoproteins are present, they disappear after the injection, and a new fraction appears that moves before the albumins.⁴ This change is caused by lipoprotein lipase.¹⁷

blood lipid data acquire significance. In Group 1 (patients with primary hypercholesterolemia) the vitamin A tolerance curve was within normal limits. In Group 2 (patients with primary or essential hyperlipemia) the vitamin A tolerance curve was always above normal, reaching a delayed and a very high peak level. (Figures that were three to five times higher than normal were found at the sixth or the ninth hours.) It came down very slowly and remained very far from the initial level at the twenty-fourth hour. In Group 3 (2 diabetic patients) the curve was very much flattened, the peak reaching a level lower than normal. In Group 4 (1 myxedematous patient) the peak level was higher than normal, but returned to within normal limits in less than 12 hours. In Group 5 (24 patients with atypical increases in blood lipids) the vitamin A tolerance curve

TABLE I. RESULTS OF VITAMIN A TOLERANCE TEST IN 19 SUBJECTS FREE OF ANY DISEASE OR TREATMENT KNOWN TO MODIFY FAT METABOLISM

19 CASES	VITAMIN A—INTERNATIONAL UNITS PER CENT OF SERUM								
	BEFORE		HOURS AFTER INTAKE OF 500,000 UNITS						
	I	II	3	6	9	12**	24	PEAK LEVEL	
Mean	94	118	1,123	1,090	576	414	166	1,498	
S.D.*	35	30	594	420	342	270	58	450	
Range {	Max.	173	173	2,600	1,749	990	775	271	2,600
	Min.	49	58	181	412	181	124	74	610

*Standard deviation.

**Figures available for 13 cases only.

TABLE II. RESULTS OF VITAMIN A TOLERANCE TEST IN 54 PATIENTS SUFFERING FROM ANGINA PECTORIS

54 CASES	VITAMIN A—INTERNATIONAL UNITS PER CENT OF SERUM								
	BEFORE		HOURS AFTER INTAKE OF 500,000 UNITS						
	I	II	3	6	9	12**	24	PEAK LEVEL	
Mean	116	139	782	2,034	1,176	709	316	2,167	
S.D.*	44	53	595	1,210	873	462	155	1,250	
Range {	Max.	247	363	2,574	5,412	4,950	4,442	3,036	5,412
	Min.	58	74	148	412	140	132	82	412

*Standard deviation.

**Figures available for 46 cases only.

was below normal in 3 cases, within normal limits in 11 cases, and above normal in 10 cases. The latter 10 cases differed from the others in having relatively high levels or heparin-sensitive lipoproteins; in 6 of them the curves were similar to those of Group 2. In Group 6 (12 patients with normal fasting blood lipids) the vitamin A tolerance curve was within normal limits in 8 cases and above normal in 4. In 2 of the latter cases the levels reached were nearly as high as those in Group 2.

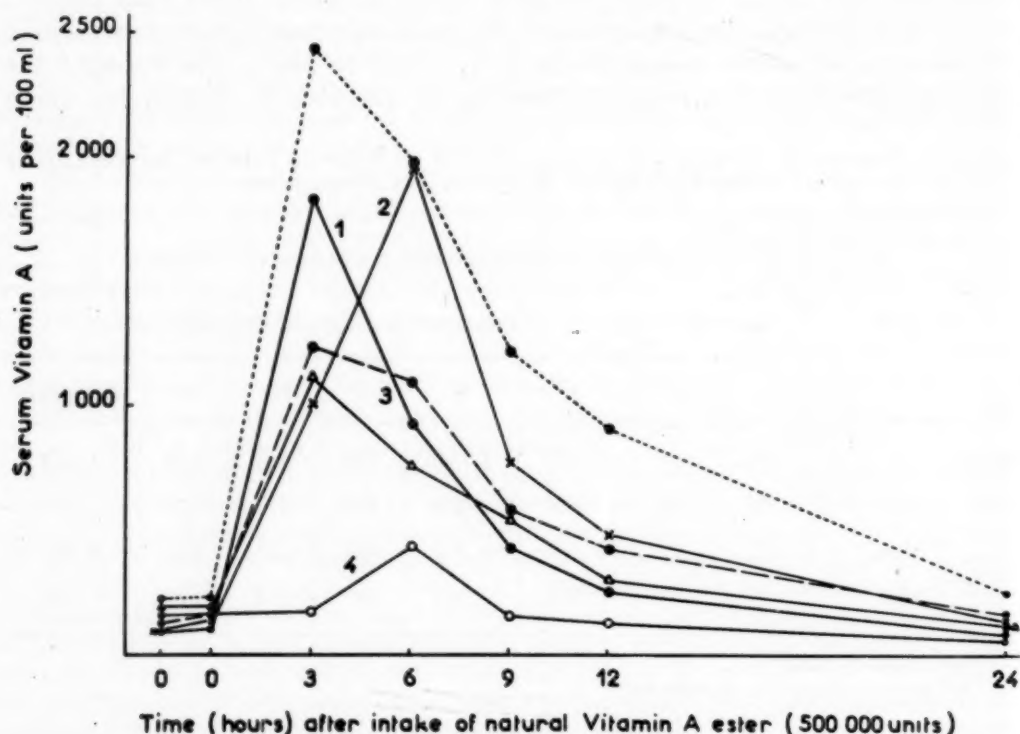


Fig. 1.—Vitamin A tolerance curves obtained in four anginal patients having: a familial hypercholesterolemic xanthomatosis (*Curve 1*); an atypical increase of blood lipids (*Curve 2*); a normal fasting blood lipid pattern (*Curve 3*); a hyperlipemia of diabetic origin (*Curve 4*). ● — — — ● Normal mean curve. ● — — — — ● Normal limit: $M + 2 S.D.$

DISCUSSION

If one accepts the fact that the vitamin A tolerance test gives evidence of the first stages of fat metabolism, its varying results in patients suffering from angina pectoris confirm the presence in these patients of several disorders of fat metabolism, and the rising of the vitamin A tolerance curve in many patients suggests that at least one of these metabolic disorders could be localized within the first stages.

The divergent results of the test in association with the pattern of the fasting blood lipids (1) differentiate between themselves the patterns of high blood lipids in diabetes, myxedema, primary hypercholesterolemia (with or without tendon xanthoma), and essential hyperlipemia, (2) point out the possibility of a frequent incidence of mild forms of the latter two diseases, (3) suggest the possibility of

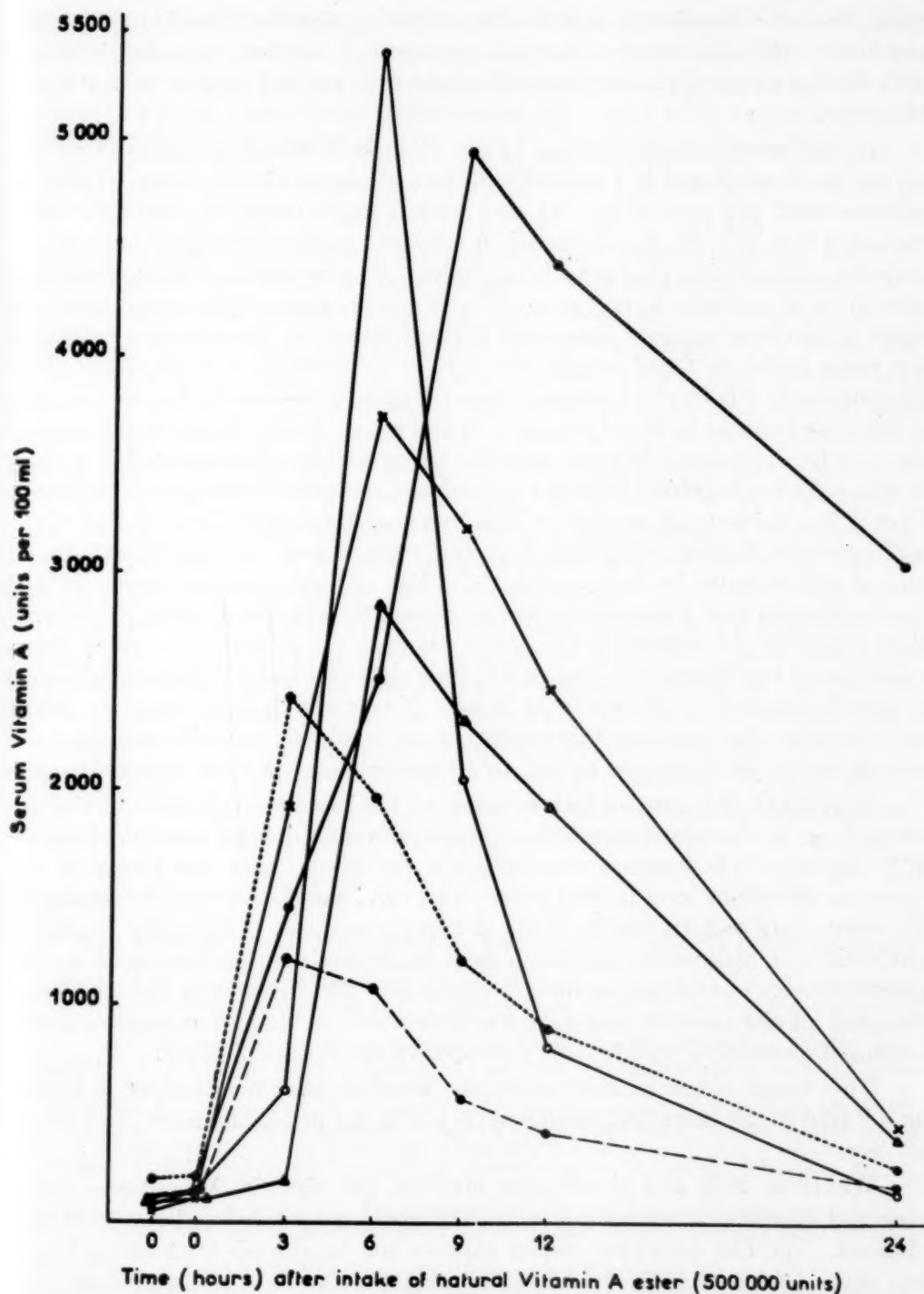


Fig. 2.—Vitamin A tolerance curves obtained in four anginal patients having: an essential hyperlipemia (curve ●—●); an atypical increase of blood lipids with relatively high levels of heparin-sensitive lipoproteins (curves △—△ and ○—○); a normal fasting blood lipid pattern (curve ×—×). ●—●—● Normal mean curve. ●—●—● Normal limit: $M + 2 S.D.$

other metabolic disorders to explain some of the atypical increases in blood lipids, and finally, (4) indicate a few subjects apparently free of any disorder, in whom both fasting blood lipids and vitamin A tolerance test are normal (8 out of the 54 cases).

In the present study the rise in the vitamin A tolerance curve above the normal limit was found in 1 patient with myxedema and in 22 others. These 22 patients (40.7 per cent of the 54) may have a single metabolic disorder. As a matter of fact, this rise in the vitamin A tolerance curve is not specific of any one disorder, since it may be found in myxedema,¹⁵ in nephrosis,¹⁸ in pancreatitis,⁷ as well as in essential hyperlipemia.^{7,11} However, none of the observations in these 22 patients suggests these first three diseases; on the contrary, many of the cases could be fitted within the pattern of essential hyperlipemia. This relatedness to a pattern of essential hyperlipemia is obvious in 8 cases (in view of the high increase in blood neutral fat) and suggestive in 10 others (because of the relative increase of heparin-sensitive lipoproteins). The remaining 4 cases in which the fasting blood lipids are normal may represent instances of the mildest form of the disease. In support of this hypothesis, one may be reminded of the well-known variability of lipemia in typical cases of essential hyperlipemia,¹⁹ and also of the presence in these patients' families of subjects who show a normal fasting lipemia and abnormal fat tolerance test.²⁰ Therefore, these 22 observations might be the expression of a single disorder, the different degrees of which might lead to an abnormally elevated lipemia either limited to the postabsorptive period or extended to the whole 24 hours. New research work would be necessary to determine whether this pattern, comparable to essential hyperlipemia, corresponds to an entity, or rather, to a syndrome arising from different causes.

Because of the various factors involved the precise mechanism of the abnormal rise in vitamin A absorption curves cannot be defined exactly. It probably concerns "chylomicron metabolism": in many cases, the return of the curve to the initial level is very slow. This fact, associated with the finding in the same cases of high fasting levels of heparin-sensitive lipoproteins (probably chylomicra or lipomicra), suggests a fault in chylomicra clearing due to an impaired activity of endogenous lipoprotein lipase. But in many of the same cases the peak of the curve is also very much delayed. This fact suggests a faulty intestinal absorption, which could also involve several mechanisms.

The results of the fat tolerance tests, whether using neutral fats or labeled ones,²¹ lead to the same discussion and do not as yet throw any more light on the subject.

Whatever their real significance may be, the vitamin A tolerance curves observed in cases of angina pectoris allow some theoretical and practical conclusions. (1) The divergent results support the hypothesis that not only one but several fat metabolic disorders may lead to coronary atherosclerosis. (2) These different metabolic disorders should be identified previous to any investigation pertaining to treatment of anginal patients with high blood lipids: a new treatment might reduce blood lipids in some cases but not in others. The return to normal of the vitamin A tolerance curve might be a better index of

therapeutic activity when a postabsorptive metabolic disorder is concerned. In such cases, a low-fat diet and heparin seem to be especially useful. (3) Some patients with such a postabsorptive disorder might escape diagnosis if only an analysis of fasting blood lipids is performed, but could be detected by an abnormal vitamin A tolerance test.

SUMMARY

Vitamin A tolerance tests were performed on 54 anginal patients with coronary atherosclerosis. In 26 of them the curves were within normal limits, in 5 they were below normal, and in 23 they were above normal. Normal curves were found in 7 patients with primary hypercholesterolemia (2 of whom had tendon xanthoma) and in 19 other patients of whom 8 had a normal blood lipid pattern and 11 had an atypical one). Flat curves occurred in 2 patients with diabetic hyperlipemia and in 3 with an atypical blood lipid pattern. High curves were found in 1 patient with myxedema and in 8 patients with primary (essential) hyperlipemia, but also in 4 with normal blood lipids and in 10 with an atypical blood lipid pattern. The different responses to the vitamin A tolerance test confirmed the presence of different metabolic disorders underlying the various hyperlipemias associated with coronary atherosclerosis. The high curves found in 22 patients (excluding the one with myxedema) are probably related to a disturbance of the early stages of lipid metabolism (absorption, transport, storage). The variable intensity of this disturbance, essentially limited to the postabsorptive period, probably accounts for the divergent results of the simple dosage of fasting blood fats. Perhaps the majority of these cases are representative of different aspects of essential hyperlipemia of variable severity. It is justifiable therefore to detect among anginal patients those with abnormally high vitamin A tolerance curves, thus allowing for a more specific treatment.

REFERENCES

1. Lenègre, J., Himbert, J., and Corcondilas, A.: Les lésions anatomiques de l'angine de poitrine commune, *Arch. mal. coeur* **51**:482, 1958.
2. Gofman, J. W., Hanig, H., Jones, H. B., Laufer, M., Lowry, E., Lewis, L., Mann, G., Moore, F., Olmstead, F., and Yeager, F.: Evaluation of Serum Lipoprotein and Cholesterol Measurements as Predictions of Clinical Complications of Atherosclerosis. Report of Cooperative Study of Lipoproteins and Atherosclerosis, *Circulation* **14**:691, 1956.
3. Lemaire, A., Cottet, J., and Ledermann, S.: Le syndrome biochimique de l'athérosclérose humaine, *Presse méd.* **64**:1129, 1956.
4. Beaumont, J. L., Beaumont, V., and Lenègre, J.: Recherches sur le métabolisme des lipides dans l'athérosclérose humaine. II, Les multiples aspects de la lipémie dans l'angine de poitrine, *Rev. franç. étud. clin. et biol.* **3**:852, 1958.
5. Gofman, J. W.: Diet in the Prevention and Treatment of Myocardial Infarction, *Am. J. Cardiology* **1**:271, 1958.
6. Raynaud, R., and Pasquet, P.: Les lipoprotéines vues sous l'angle de l'électrophorèse sur papier, Abstracts of Symposia, p. 389, Third World Congress of Cardiology, Brussels, 1958.
7. Deuel, H. J.: The Lipids, New York, 1955, Interscience Publishers, Inc.
8. Ganguly, J., Krinsky, N. I., Mehl, J. W., and Deuel, H. J.: Studies of the Distribution of Vitamin A on Ester and Alcohol and of Carotenoids in Plasma Proteins of Several Species, *Arch. Biochem.* **38**:275, 1952.
9. Adlesberg, D.: Fat and Vitamin A Absorption in Sprue, *New York J. Med.* **44**:604, 1944.
10. Barnes, B. C., Wollaeger, E. E., and Mason, H. L.: Comparative Absorption of Vitamin A From Water Miscible and Oily Preparation by Normal Adults and Patients With Steatorrhea, *J. Clin. Invest.* **27**:982, 1950.

11. Martt, J. M., and Connor, W. E.: Idiopathic Hyperlipemia Associated With Coronary Atherosclerosis, *A.M.A. Arch. Int. Med.* **97**:492, 1958.
12. Beaumont, J. L., and Ardaillou, R.: L'épreuve d'hypervitaminémie A provoquée, *Rev. franç. étud. clin. et biol.* **4**:40, 1959.
13. Embree, N. D., Ames, S. R., Lehmann, R. W., and Harris, P. L.: Determination of Vitamin A. *In* Glick, D.: *Methods of Biochemical Analysis*, Vol. 4, New York, 1957, Interscience Publishers, Inc., p. 43.
14. Week, E. F., and Sevigne, F. J.: Vitamin A Utilization Studies; Utilization of Vitamin A Alcohol, Vitamin A Acetate, and Vitamin A Natural Ester by Humans, *J. Nutrition*, **40**:563, 1950.
15. Bonfils, S., and Marnay, C.: Résultats de l'épreuve d'hypervitaminémie A provoquée chez les sujets normaux et pathologiques, *Compt. rend. Soc. de Biol. Paris* **142**:29, 1948.
16. Beaumont, J. L., Ardaillou, R., and Lenègre, J.: Recherches sur le métabolisme des lipides dans l'athérosclérose humaine. III, L'épreuve d'hypervitaminémie A provoquée, *Rev. franç. étud. clin. et biol.* **3**:1045, 1958.
17. Anfinsen, C. B.: Lipoprotein Metabolism in the Etiology of Atherosclerosis, *Minnesota Med.* **38**:731, 1955.
18. Kagan, M. B., Thomas, E. M., and Jordan, D. A.: Serum Vitamin A and Total Plasma Lipid Concentrations as Influenced by the Oral Administration of Vitamin A to Children With the Nephrotic Syndrome, *J. Clin. Invest.* **29**:141, 1950.
19. Thannhauser, S. J.: *Lipidoses: Diseases of the Intracellular Lipid Metabolism*, Ed. 3, New York, 1958, Grune & Stratton, Inc.
20. Wilkinson, C. E., Jr.: Spaced Fat Feeding. A Regimen of Management for Familial Hyperlipemia, *Ann. Int. Med.* **45**:674, 1956.
21. Likoff, W., Berkowitz, D., Woldow, A., Gerson Jacobs, A., and Sklaroff, D. M.: Radioactive Fat Absorption Patterns. Their Significance in Coronary Artery Atherosclerosis, *Circulation* **18**:1118, 1958.

Digoxin: Single Versus Divided Daily Maintenance Dosage

*Gerard Church, M.B., Ch.B. (Glas.), and Henry J. L. Marriott, M.D.
Baltimore, Md.*

Several authorities have recently recommended that the relatively rapid, short-acting glycoside digoxin is the preparation of choice in the treatment of heart failure when the therapeutic range is narrow.¹⁻³ Because the end-point of full digitalization is often not clear-cut, dosage of the drug is frequently pushed to toxicity in order to be certain that the patient is deriving maximal benefit. Using such a glycoside as digoxin may make it easier and safer to maintain a patient nearer to the toxic level than will the use of slower, longer-acting preparations. Digoxin is available in 0.5 mg. and 0.25 mg. tablets* and is frequently prescribed as a single 0.5 mg. tablet for daily maintenance. Most patients probably find a single dose more convenient and easier to remember, but on this schedule, toxicity sometimes occurs and necessitates revision of dosage. Because of tablet size the most convenient reduction is a halving of the dose to 0.25 mg. daily, which is frequently inadequate for satisfactory maintenance.

Batterman⁴ has stated that when a patient becomes intoxicated with digoxin, he can often continue on the same total daily dose, but divided, and have all the signs and symptoms of toxicity promptly subside. However, he has more recently made the apparently conflicting assertion that the intoxicating dose of digoxin is the same whether the drug is given in a divided or in a single daily dose, and he has concluded that an undivided single daily dose is "always the most satisfactory way of administering" this preparation.⁵ The properties of digoxin favor acceptance of his earlier observation and invite re-examination of his later conclusions. A priori it would seem likely that dividing the daily dose of this drug would achieve smoother maintenance.

Friedman² has compared digitalis with insulin. Applying this analogy, one may say that, when the patient is fluctuating between toxicity and inadequate control, the giving of digoxin in a single daily dose, in place of a longer-acting preparation such as digitoxin, parallels the inappropriate administration to a brittle diabetic of a single daily dose of regular insulin rather than a single dose of protamine insulin.

From the Departments of Medicine, Mercy Hospital, and University of Maryland School of Medicine, Baltimore, Md.

Aided by a grant from Burroughs Wellcome & Company, Inc.

Received for publication March 4, 1959.

*Lanoxin, Burroughs Wellcome & Company, Inc.

The present study was undertaken to determine whether digoxin is in fact tolerated differently in a divided than in a single daily dose.

METHOD

Thirty outpatients who were on maintenance digitalis schedules with other preparations were switched to digoxin, 0.25 mg. twice daily, without altering adjunctive therapy. Weekly interviews and examinations were conducted in order to confirm satisfactory maintenance or uncover evidence of toxicity. If after 4 weeks no toxic symptoms or signs had developed, the total daily dose (0.5 mg.) was given each morning. If after a further 4 weeks no toxicity had developed, the dose was increased by adding 0.25 mg. in the evening; if this was tolerated, the new total dose (0.75 mg.) was given in one morning dose. If in turn this proved nontoxic, 0.25 mg. was again added as an evening dose. If this uneven division (0.75 mg. + 0.25 mg.) was tolerated, 1.0 mg. was then given in a single morning dose; but if not, then even division (0.5 mg. + 0.5 mg.) was attempted.

Evidence of intolerance to an undivided schedule was accepted when toxic symptoms appeared within 2 to 3 days and then disappeared within a similar period on resumption of the divided schedule. In the absence of toxicity, all dosage systems were continued for 4 weeks before a further increase was attempted.

Some patients were unable to follow instructions or were indefinite in their symptomatology. These were discarded from the study. Because patients were seen only at weekly intervals, the occurrence of cardiotoxicity was impossible to evaluate; therefore, only symptoms referable to the gastrointestinal and central nervous systems could be used as evidence of intolerance.

TABLE I.

PATIENT	AGE (YR.) RACE SEX	TYPE OF HEART DISEASE	TOLERATED DOSE (MG.)	TOXIC DOSE (MG.)	TOXIC EFFECTS
G.R.	60 W, M	Coronary	0.5 + 0.25	0.75	Drowsiness
A.W.	56 N, M	Syphilitic aortic insufficiency	0.5 + 0.25	0.75	Nausea and vomiting
E.R.	58 W, F	Rheumatic mitral and aortic	0.5 + 0.25	0.75	Dizziness
R.P.	61 N, F	Hypertensive and arteriosclerotic	0.5 + 0.25	0.75	Nausea and vomiting
L.B.	47 W, F	Rheumatic mitral	0.25 + 0.25	0.5	Nausea

RESULTS

Five patients proved able to tolerate a divided daily dose of digoxin, but were unable to take the same total daily dose at one time without toxicity. These results are summarized in Table I. In addition, one patient was able to take 1 mg. daily when it was divided as 0.5 mg. in the morning and 0.5 mg. in the evening, but when it was unevenly divided as 0.75 mg. in the morning and 0.25 mg. in the evening, he developed anorexia, abdominal pain, and blurred vision.

DISCUSSION AND CONCLUSIONS

Our results indicate that some patients can be maintained on a higher total daily amount of digoxin if this is administered in divided doses. To achieve optimal maintenance in such patients, it seems that the drug should be given

in divided doses, and that Batterman's categorical statement that a single dose is "always the most satisfactory way of administering" digoxin is unacceptable.

It is, of course, not easy to establish in outpatients which maintenance schedule is more satisfactory, for outpatient management is subject to many variables, such as the sodium intake, amount of exercise, the weather, and the regularity with which the patient remembers to take his medication. In our opinion, such factors could explain Batterman's surprising finding that a patient can develop heart failure on a larger divided daily dose when changed from a smaller single dose (e.g., from 0.75 mg. once daily to 0.5 mg. twice daily; or from 1.0 mg. once daily to 0.5 mg. three times a day). We have not encountered such cases and we have observed no tendency for congestive signs and symptoms to worsen when a divided schedule is substituted for an undivided one.

On the other hand, it is theoretically possible that with a single daily dose of a short-acting glycoside the patient may attain better cardiac reserve during the earlier part of the day, only to lose it during the later part of the day; but, since the exercise load during the later part of the day is less, he may not suffer significant disability at this time. We cannot, however, believe that there can be any great *therapeutic* difference between the two schedules, although it seems definite that the risk of toxicity is significantly greater on the single dose schedule. It is therefore our conclusion that in the majority of cases maintenance is effectively and more safely controlled on a divided schedule. If on this schedule control is not adequate, then it would seem preferable to change to a long-acting preparation.

SUMMARY

Some recent reports on digoxin dosage are reviewed. A short clinical study, designed to resolve the somewhat conflicting evidence, has failed to support certain previous recommendations.

It was found that some patients could be satisfactorily maintained on a higher daily dose of digoxin if this was given in divided doses. To minimize toxicity and achieve optimal maintenance in the majority of patients, the daily dose is probably best administered in this way.

REFERENCES

1. Lown, B., and Levine, S. A.: *Current Concepts in Digitalis Therapy*, Boston, 1954, Little, Brown and Company.
2. Friedman, M.: Digitalis Therapy and Intoxication, *Mod. Concepts Cardiovas. Dis.* **25**:311, 1956.
3. Sodeman, W. A.: Problems in the Bedside Management of Digitalis. *In* *Digitalis*, Edited by E. G. Dimond, Springfield, Ill., 1958, Charles C Thomas, pp. 158-165.
4. Batterman, R. C., and DeGraff, A. C.: Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin and Lanatoside C, for the Management of Ambulatory Patients With Congestive Heart Failure, *AM. HEART J.* **34**:663, 1947.
5. Batterman, R. C.: Observations on the Clinical Use of Digitalis. *In* *Digitalis*, Edited by E. G. Dimond, Springfield, Ill., 1958, Charles C Thomas, pp. 117-157.

The Hemodynamic Results of Surgery for Aortic Stenosis

William L. Kraus, M.D., Robert C. Schlant, M.D.,** Charles B. Moore, M.D.,*** Donald S. Dock, M.D.,**** Edward Woodward, Jr., M.D.,***** Florence W. Haynes, Ph.D., and Lewis Dexter, M.D., Boston, Mass.*

The surgical relief of aortic stenosis has been attempted by a variety of techniques over the past several years.¹⁻³ For a number of reasons, this operation has presented much greater problems to the surgeon than has mitral valvuloplasty. The patients are generally older, the surgical approach is difficult, and the valve cusps are heavily calcified, deformed, and fused. Unless extreme care is taken when the valve is fractured, a disastrous degree of regurgitation may be readily produced. Despite these obstacles, aortic valvuloplasty has, in the hands of several experienced surgeons, come to be performed with increasing frequency.⁴⁻⁸ Although there are several reports on the subjective value of surgery for aortic stenosis,⁹⁻¹⁴ the literature to date contains few critical evaluations of its objective hemodynamic effects.^{15,16}

The present study was undertaken in cooperation with the Thoracic Surgical Service in order to quantify by pre- and postoperative left heart catheterization the hemodynamic effects of transaortic aortic valvuloplasty as performed by Dr. Dwight E. Harken. The surgical technique and experience with this procedure have been reported elsewhere.^{17,18}

MATERIAL AND METHODS

Left heart catheterization was performed before and after aortic valvuloplasty in 19 patients, of whom 3 (Tables I and II, Patients 14, 15, 16) underwent mitral valvuloplasty at the same time. Patients were selected for preoperative left heart catheterization in order to assess the severity of the aortic stenosis. Postoperatively, they were selected primarily on the basis of laboratory availability. The postoperative studies were performed between the fifth and twenty-

From the Departments of Medicine, Peter Bent Brigham Hospital, and Harvard Medical School, Boston, Mass.

This work was supported in part by grants from the Life Insurance Medical Research Fund, the National Heart Institute, U. S. Public Health Service (Grant No. H-450), and the American Heart Association.

Received for publication April 6, 1959.

*Postdoctoral Research Fellow, Life Insurance Medical Research Fund.

**Work done during the tenure of a Research Fellowship from the American Heart Association. Present address: Department of Medicine, Emory University, Atlanta, Ga.

***Work done during the tenure of a Research Fellowship from the Massachusetts Heart Association. Present address: Ochsner Clinic, New Orleans, La.

****Research Fellow, American Heart Association.

*****Postdoctoral Research Fellow, National Heart Institute, U. S. Public Health Service.

second postoperative days in 17 patients; one patient was studied 161 days, and another was studied 432 days, after surgery. Patients 9-12, 16, 18, and 19 were the most recently studied and represent a consecutive surgical series. The salient clinical data are presented in Table I.

All patients had severe aortic stenosis. On the basis of both clinical and catheterization findings (Tables I and II), they were classified as follows: aortic stenosis the only significant lesion (6 patients, Patients 1-6); aortic stenosis and "insignificant" aortic regurgitation (7 patients, Patients 7-13); aortic stenosis, significant mitral stenosis, and "insignificant" aortic regurgitation (3 patients, Patients 14-16); aortic stenosis, significant mitral regurgitation, and "insignificant" aortic regurgitation (2 patients, Patients 17 and 18); apparently pure aortic stenosis, but severe coronary artery disease found at surgery (1 patient, Patient 19).

Left heart catheterization was performed by the posterior transthoracic route as described previously.¹⁹ Repeated measurements of pressures in the left atrium, left ventricle, and brachial artery were made. Cardiac output was determined by the indicator dilution method,²⁰ employing left atrial injection of I¹³¹-tagged human serum albumin. Brachial arterial systolic mean pressures and left ventricular systolic ejection mean pressures were obtained by planimetry of simultaneously recorded pressure tracings.

The brachial arterial systolic upstroke time was measured from the onset of the upstroke to the maximum pressure peak and was corrected for pulse rate by dividing by the square root of the cycle length¹³ as follows:

$$\text{Corrected upstroke time} = \frac{\text{Observed upstroke time}}{\sqrt{\text{R-R interval}}}$$

The normal value is 0.10 to 0.16 second.¹³

The brachial arterial systolic upstroke slope was measured on the steepest portion of the upstroke, prior to the anacrotic notch, and expressed in millimeters of mercury per second (normal = 750 to 1,250 mm. Hg/second).¹³

Aortic valve areas were calculated by the Gorlin formula²¹:

$$A = \frac{\dot{V}}{44.5 \times R \times \text{SEP} \times \sqrt{LV_{sm} - BA_{sm}}}$$

where A = Cross-sectional area of aortic valve in sq. cm.

\dot{V} = Cardiac output, i.e., aortic flow, in ml./min.

44.5 = $\sqrt{2 \times \text{gravity acceleration}} = \sqrt{2 \times 980} = \sqrt{1,960}^*$

R = Pulse rate

SEP = Systolic ejection period, measured from the brachial arterial pressure curve* in sec./beat

LV_{sm} = Left ventricular systolic ejection mean pressure, in mm. Hg

BA_{sm} = Brachial arterial systolic mean pressure, in mm. Hg

Mitral valve areas were calculated by the Gorlin formula, employing an empirical constant of 38.6, ventricular diastolic filling period measured from the left ventricular pressure tracings, and the diastolic mean pressures in the left atrium and ventricle. A constant of 31 is used when the diastolic filling period is measured from the brachial arterial pressure curve, mean pulmonary "capillary" pressure is substituted for left arterial pressure, and left ventricular diastolic mean pressure is assumed to be 5 mm. Hg.

Valvular regurgitation was estimated by analysis of the indicator dilution curves, using a modification of the method of Korner and Shillingford.²² The following arbitrary classification was used:

*In a previously reported study on left heart catheterization in aortic stenosis¹⁹ an empirical constant of 38.5 and left ventricular systolic ejection period were employed. Experience in the interval has shown the brachial arterial systolic ejection period to be a more reliable and reproducible measurement than the left ventricular, the systolic portion of left ventricular pressure tracings being more susceptible to distortion by damping.

Calculated regurgitant flow equal
to or greater than forward flow = 4+ regurgitation
Calculated regurgitant flow
75-99 per cent of forward flow = 3+ regurgitation
Calculated regurgitant flow
50-74 per cent of forward flow = 2+ regurgitation
Calculated regurgitant flow
25-49 per cent of forward flow = 1+ regurgitation
Calculated regurgitant flow less
than 25 per cent of forward flow = \pm regurgitation

RESULTS

The findings at pre- and postoperative left heart catheterization are presented in Table II.

Cardiac Index.—Preoperatively, the 6 patients with pure aortic stenosis had an average cardiac index of 3.4 liters per minute per square meter (range, 2.8 to 5.0). One other patient (Patient 19) with clinically pure aortic stenosis, but with a preoperative cardiac index of 2.5 L./min./M.², was found at surgery to have visibly and palpably sclerotic coronary arteries. The preoperative cardiac index was below 2.9 L./min./M.² in 8 of the 12 patients with associated "insignificant" aortic regurgitation, including the 3 patients with mitral stenosis and 1 of the 2 with mitral regurgitation.

Postoperatively, the cardiac index showed no significant change in 5 of the 6 patients with pure aortic stenosis (Patients 1-5) and decreased from 2.8 to 1.5 L./min./M.² in Patient 6. The cardiac index decreased significantly in 3 of the 7 patients with associated "insignificant" aortic regurgitation alone (Patients 7, 8, 10) but increased in Patient 9. There was no significant change in the cardiac index postoperatively in the 5 patients (Patients 14-18) with associated mitral disease, except in Patient 17, whose index increased from 3.1 to 3.9 L./min./M.². Patient 19, with pure aortic stenosis and coronary artery disease, had a decrease in cardiac index from 2.5 to 1.9 L./min./M.². In the entire group of 19 patients, there was no significant change postoperatively in 12 patients, and a variable change in the other 7 patients.

The stroke index was essentially unchanged postoperatively in 14 patients and was variably reduced in 5 (Patients 1, 6, 7, 8, 19), all of whom had a decreased cardiac index and, except for Patient 6, a more rapid pulse rate postoperatively.

Pressures.—The left ventricular systolic peak pressure preoperatively ranged from 144 to 264 mm. Hg and fell postoperatively in all patients. The left ventricular systolic ejection mean pressure fell in all but Patient 10, in whom it remained unchanged, despite a fall of 45 mm. Hg in systolic peak pressure. This was due to a marked change in contour of the left ventricular pressure curve.

The preoperative brachial arterial systolic, diastolic, and pulse pressures were not related to the severity of the narrowing of the aortic valve. The brachial arterial pulse pressure preoperatively ranged from 26 to 75 mm. Hg, averaging 50 mm. Hg. Postoperatively, the brachial arterial pressure showed no consistent change in systolic peak or mean levels. In 15 patients the diastolic pressure in the brachial artery fell an average of 12 mm. Hg. The brachial arterial pulse pressure increased postoperatively in 13 patients, an average of 12 mm. Hg, and

decreased in 6 patients, an average of 15 mm. Hg. No widening of the pulse pressure was observed in Patients 7-18, in whom the degree of aortic regurgitation was considered "insignificant."

The mean systolic pressure difference across the aortic valve during ejection ranged from 29 to 113 mm. Hg before operation and was reduced after surgery in all patients. It was completely eliminated only in Patient 15. In the others, from 29 to 92 per cent of the preoperative pressure difference persisted postoperatively.

The left ventricular end-diastolic pressures ranged preoperatively from 1 to 32 mm. Hg and postoperatively from 4 to 50 mm. Hg, with an increase in 8 patients and a decrease or no essential change in 11 patients.



Fig. 1.—Pre- and postoperative findings of calculated aortic valve area. The horizontal line is drawn at the "critical valve area" of 0.7 sq. cm., above which virtually all patients are asymptomatic.

Brachial Arterial Pressure Pulse Contour.—Preoperatively, the brachial arterial pressure tracing in all patients showed contour changes commonly associated with aortic stenosis, i.e., prolonged systolic upstroke time and/or flat upstroke slope with anacrotic notches of varying height and distinctness.

After surgery, the upstroke time became shorter in 11 patients and showed no significant change in the other 8. The upstroke slope became steeper in 16, flatter in 2, and showed no significant change in 1. In Patient 15 the transaortic pressure difference was abolished, with production of clinically significant regurgitation. These events were reflected in marked changes in the arterial pressure tracing: the rate-corrected upstroke time fell from 0.20 to 0.08 second per beat, and the upstroke slope increased from 477 to 3,220 mm. Hg per second. In the others, however, there was no correlation between the degree of change in upstroke time or slope and the surgically produced alterations of aortic valve area, stroke index, or other measured parameters.

Stroke Work.—The stroke work, calculated using only the net forward stroke flow, decreased postoperatively in 12 patients and showed no significant change in the other 7. There was no apparent relationship between stroke work and left ventricular end-diastolic pressures pre- or postoperatively.

TABLE I

PATIENT NUMBER, NAME	AGE, SEX	N. Y. HEART ASSN. CLASS.	SYMPTOMS					PHYSICAL FINDINGS					RADIOLOGIC FINDINGS								
			ANGINA	SYNCOPE	DYSPNEA	ORTHOPNEA	PAROXYSMAL NOCTURNAL DYSPNEA	CAROTID PULSE	GRADE OF MURMUR				AORTIC SECOND SOUND	OVER-ALL ENLARGEMENT (%)	LEFT VENTRICLE	LEFT ATRIUM	PULMONARY VASCULAR MARKINGS	AORTA	VALVULAR CALCIFICATION		
									AORTIC SYSTOLIC	AORTIC DIASTOLIC	MITRAL SYSTOLIC	MITRAL DIASTOLIC									
<i>Aortic Stenosis, Pure</i>																					
1. J.J.	53, M	II	0	0	+	+	+	+	P	IV	0	0	0	-	+20	+	N	N	Aortic		
2. V.L.	39, F	II	0	0	+	+	+	+	P	V	0	0	0	0	+12	+	N	N	Aortic		
3. R.G.	55, F	II-III	0	0	+	+	+	+	P	IV	0	0	0	0	+20	+	N	N	Aortic		
4. J.I.	55, M	III	0	0	+	+	+	+	P	III	0	0	0	0	+20	+	N	N	Aortic		
5. G.R.	25, M	I	0	0	+	+	+	+	P	IV	0	0	0	0	0	+	N	N	Aortic		
6. D.B.	30, M	II-III	0	0	+	+	+	+	P	V	0	0	0	I	+12	+	N	++	Aortic		
<i>Aortic Stenosis and Clinically "Insignificant" Aortic Regurgitation</i>																					
7. E.B.	37, F	II	0	0	+	+	+	+	P	IV	III	?	0	0	+20	+	N	N	Aortic		
8. P.M.	30, M	I	0	0	+	+	+	+	P	V	III	0	0	0	+30	+	N	N	Aortic		
9. A.E.	45, F	II	0	0	+	+	+	+	B	IV	II	0	0	0	+20	+	N	N	Aortic		
10. V.D.	31, M	III	0	0	+	+	+	+	P	III	I	0	0	0	+12	+	N	N	0		
11. K.W.	56, M	III	0	0	+	+	+	+	P	IV	III	0	0	0	+23	+	N	N	Aortic		
12. J.D.	39, M	II-III	0	0	+	+	+	+	B	III	II	0	0	0	0	+	N	N	Aortic		
13. F.M.																					

<i>Aortic Stenosis, Mitral Stenosis, and Clinically "Insignificant" Aortic Regurgitation</i>													
14. F.M.	41, F	III	+	0	++	+	+	+	+	+	+	Small	0
15. A.I.	53, F	III	+	±	+	+	+	+	+	+	+	N	0
16. M.S.	41, F	II	0	0	0	0	0	0	+	+	+	N	Aortic and mitral
<i>Aortic Stenosis, Mitral Regurgitation, and Clinically "Insignificant" Aortic Regurgitation</i>													
17. F.Gr.	49, M	III	+	0	+	0	0	+	+	+	+	N	Aortic and mitral
18. F.Ge.	53, M	III	+	0	+	+	+	+	+	+	±	N	Aortic
<i>Aortic Stenosis and Coronary Artery Disease</i>													
19. C.W.	59, M	III	+	0	+	+	+	+	+	+	+	+	Aortic

Carotid Pulse: P = Plateau. B = Bisferiens. Radiologic Findings: N = Normal. - = Diminished. + = Increased. 0 = Absent.

TABLE II

PATIENT NUMBER	NAME	AGE, SEX	SECOND STUDY (DAYS POSTOP.)	H. S. A. (M. ²)	CARDIAC INDEX (L./MIN./M. ²)	REGURGITATION	PULSE	STROKE INDEX (C.C./BEAT/M. ²)	STROKE WORK (GM. M./BEAT/M. ²)	BRACHIAL ARTERIAL PRESSURE CONTOUR			PRESSURES (MM. Hg)						TRANSVALVULAR MEAN PRESSURE DIFFERENCE (MM. Hg)	AORTIC VALVE AREA ** (CM. ²)				
										RATE-CORRECTED TIME (SEC.)	SYSTOLIC UPSTROKE SLOPE (MM. Hg/SEC.)	SYSTOLIC EJECTION PERIOD (SEC./BEAT)	BRACHIAL ARTERY			LEFT VENTRICLE					LEFT ATRIUM			
													SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC MEAN	SYSTOLIC	END-DIASTOLIC				SYSTOLIC EJECTION MEAN	DIASTOLIC MEAN	DIASTOLIC MEAN
1.	J.J.	53, M	18	1.74	5.0	0	88	56	153	.25	610	.38	134	79	103	117	264	32	222	24	24	105	0	0.6
2.	V.L.	39, F	7	1.74	4.3	0	110	39	90	.18	1,030	.26	169	110	126	146	212	21	182	13	13	36	0	1.0
3.	R.G.	55, F	17	1.62	3.9	0	120	33	79	.20	456	.28	94	64	75	83	220	7	175	2	—	92	—	0.4
				1.58	3.9	0	110	35	81	.12	640	.26	92	56	73	81	196	4	166	4	—	85	0	0.5
4.	J.I.	55, M	15	1.47	3.0	2+*	74	41	118	.26	395	.32	148	86	109	123	254	8	211	2	2	88	0	0.4
				1.45	3.5	±	96	36	80	.25	523	.31	148	74	100	126	212	11	165	6	6	39	0	0.6
5.	G.R.	25, M	19	1.78	3.1	0	105	29	80	.21	566	.30	111	74	86	97	254	20	210	10	10	113	0	0.4
				1.76	3.4	0	106	32	50	.20	630	.32	117	58	80	93	190	50	144	19	19	51	0	0.6
6.	D.B.	30, M	20	2.06	2.9	0	81	36	75	.19	228	.35	99	73	83	89	199	13	159	10	—	70	—	0.6
				2.00	3.2	0	100	32	50	.19	318	.28	99	72	85	90	135	9	118	6	6	28	0	1.0
				2.04	2.8	3+*	88	32	80	.15	344	.38	104	68	83	90	256	19	196	12	12	106	0	0.4
				1.96	1.5	±	66	23	30	.13	407	.28	69	45	56	60	163	21	110	17	17	50	0	0.5

Aortic Stenosis, Pure

Aortic Stenosis and Clinically "Insignificant" Aortic Regurgitation

7. E.B.	37, F	11	1.58	5.2	1+	106	49	122	.21	531	.35	110	59	75	101	251	10	186	6	15	85	9	0.7	3.2
			1.55	2.0	1+	127	16	25	.10	792	.22	90	52	66	79	181	20	129	15	17	50	2	0.5	—
8. P.M.	30, M	16	1.55	3.9	1+	95	41	113	.30	288	.32	127	80	96	109	258	20	210	18	18	101	0	0.4	—
			1.50	2.5	1+	106	24	43	.13	794	.29	110	57	78	95	185	20	146	14	14	51	0	0.4	—
9. A.E.	37, M	15	1.95	2.1	±	80	26	53	.16	440	.35	101	61	78	87	205	11	154	11	11	67	0	0.5	—
			1.84	3.1	±	104	30	50	.13	1,543	.26	124	58	78	95	169	17	133	15	15	38	0	0.8	—
10. V.D.	45, F	16	1.50	2.6	1+	154	17	29	.21	986	.21	112	67	84	92	170	1	121	1	1	29	0	0.5	—
			1.52	1.8	2+	81	22	31	.19	846	.31	113	55	73	98	125	25	121	23	23	23	0	0.5	—
11. K.W.	31, M	17	1.82	2.8	3+	94	30	65	.26	480	.34	113	75	87	100	187	8	161	6	6	62	0	0.5	—
			1.73	3.0	1+	115	26	52	.17	1,462	.30	119	69	87	99	185	12	152	8	8	53	0	0.5	—
12. J.D.	56, M	17	1.80	2.0	1+	78	26	59	.25	365	.34	123	64	82	104	161	12	136	11	12	32	1	0.5	—
			1.76	1.8	±	87	21	28	.23	614	.36	130	48	78	98	132	18	115	12	16	17	4	0.6	1.5
13. F.M.	39, M	432	1.69	3.4	1+	109	32	64	.22	461	.30	123	75	95	107	181	4	152	3	3	45	0	0.6	—
			1.68	3.2	±	105	31	59	.23	559	.32	133	79	100	115	162	4	144	0	0	29	0	0.7	—

Aortic Stenosis, Mitral Stenosis, and Clinically "Insignificant" Aortic Regurgitation

14. F.M.	41, F	161	1.43	2.3	0	82	28	66	.25	544	.31	137	89	105	123	188	9	172	6	15	49	9	0.4	1.0
			1.48	2.3	0	70	33	56	.22	1,070	.28	117	72	95	111	149	11	130	6	9	19	3	0.9	1.7
15. A.I.	53, F	5	1.66	2.4	0	74	33	61	.20	477	.32	122	64	85	107	148	8	138	5	16	31	11	0.7	0.9
			1.57	2.5	2+	94	26	38	.08	3,220	.28	137	57	87	112	123	11	112	7	10	0	3	—	2.0
16. M.S.	41, F	22	1.65	2.4	1+	95	25	45	.25	441	.27	98	62	75	89	145	5	130	5	20	41	15	0.5	0.9
			1.59	2.6	±	95	27	43	.19	1,633	.25	114	65	94	103	138	12	122	8	14	19	6	0.9	1.7

TABLE II—CONT'D

PATIENT NUMBER	NAME	AGE, SEX	SECOND STUDY (DAYS POSTOP.)	H. S. A. (M. ²)	CARDIAC INDEX (L./MIN./M. ²)	REGURGITATION	PULSE	STROKE INDEX (C.C./BEAT/M. ²)	STROKE WORK (GM. M./BEAT/M. ²)	BRACHIAL ARTERIAL PRESSURE CONTOUR			PRESSURES (MM. HG.)										TRANSVALVULAR MEAN PRESSURE DIFFERENCE (MM. HG.)		VALVE AREA** (CM. ²)	
										RATE-CORRECTED	SYSTOLIC UPSTROKE	TIME (SEC.)	SYSTOLIC UPSTROKE	SLOPE (MM. HG./SEC.)	SYSTOLIC EJECTION	BRACHIAL ARTERY				LEFT VENTRICLE				LEFT ATRIUM	AORTIC	MITRAL
																SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC MEAN	SYSTOLIC	END-DIASTOLIC	SYSTOLIC EJECTION MEAN	DIASTOLIC MEAN			

17.	F.Gr.	49, M	13	1.71 1.66	3.1 3.9	1+ 0	84 115	37 34	75 58	.21 .15	656 1,500	.33 .26	141 126	66 63	92 78	112 99	188 137	16 3	157 122	8 —	25 21	45 23	17 22	0.6 1.0	1.1 1.3
18.	F.Ge.	53, M	21	1.91 1.86	2.5 2.8	2+ 1+	84 91	29 31	46 48	.25 .21	507 536	.38 .32	123 124	58 64	82 84	96 102	144 136	15 10	125 119	9 5	12 8	29 17	3 3	0.6 1.0	2.9 3.1

Aortic Stenosis, Mitral Regurgitation, and Clinically "Insignificant" Aortic Regurgitation

19.	C.W.	59, M	21	2.04 2.00	2.5 1.9	0 0	88 111	29 17	74 19	.25 .23	439 293	.31 .21	156 85	90 63	104 67	132 76	239 119	8 16	187 92	5 14	5 14	55 16	0 0	0.6 1.0	— —
-----	------	-------	----	--------------	------------	--------	-----------	----------	----------	------------	------------	------------	-----------	----------	-----------	-----------	------------	---------	-----------	---------	---------	----------	--------	------------	--------

Aortic Stenosis and Coronary Artery Disease

Aortic Stenosis and Coronary Artery Disease

*No evidence of valvular regurgitation clinically.

**Calculation based on forward flow only. This underestimates anatomic orifice in presence of regurgitation.

B.S.A.: Body surface area, in square meters.

Aortic Valve Area.—(Fig. 1.) The changes in calculated aortic valve area are summarized as follows:

- 1 patient 0.7 sq. cm. to normal (regurgitation produced)
- 5 patients 0.6 to 1.0 sq. cm.
- 1 patient 0.4 to 0.9 sq. cm.
- 1 patient 0.5 to 0.9 sq. cm.
- 1 patient 0.5 to 0.8 sq. cm.
- 2 patients 0.4 to 0.6 sq. cm.
- 1 patient 0.6 to 0.7 sq. cm.
- 1 patient 0.5 to 0.6 sq. cm.
- 2 patients 0.4 to 0.5 sq. cm.
- 3 patients no change (0.4, 0.5, 0.6 sq. cm.)
- 1 patient 0.7 to 0.5 sq. cm. (decrease)

Changes of 0.1 square centimeter may be considered insignificant. On the basis of this criterion, the calculated aortic valve area was increased after surgery in 11 of the 19 patients. In 9 patients the postoperative area was above the critical level of 0.7 sq. cm. Four of the 7 most recently operated upon consecutive patients (Patients 9-12, 16, 18, 19) had postoperative valve areas of 0.9, 0.9, 1.0, and 1.0 sq. cm.

DISCUSSION

The cross-sectional area of the normal aortic valve orifice in systole is 2.6 to 3.5 square centimeter.²³ With the development of stenosis, the hemodynamic consequences are related as follows:

$$A = \frac{F}{K \sqrt{\Delta P}} \quad (21)$$

where A = Cross-sectional area of the aortic valve orifice

K = An empirical constant

F = Flow across the valve during systole

ΔP = Difference between left ventricular and aortic mean systolic pressures during ejection

I. Stages of the Disease.—

A. *Asymptomatic:* It has been shown, both clinically and theoretically, that progressive narrowing of the aortic valve produces little if any clinical disability until the orifice is reduced to approximately one fourth of its original size.²³ Up to this point the patient is essentially asymptomatic, short of violent exercise.

B. *Symptomatic, Compensated:* Once the valve area has been reduced to 0.7 sq. cm. or less, however, the classic triad of angina, syncope, and left ventricular failure appears.¹⁹ The patient, although symptomatic, is still able to remain in a compensated state on medical management. The cardiac output at this stage of pure aortic stenosis remains normal or even high, as exemplified by Patients 1-6 in this series. Considering the orifice formula, it is evident that this can be achieved only at the expense of marked elevation of left ventricular systolic pressure. Left ventricular work (pressure \times flow) is greatly increased. This burden is well sustained by extreme hypertrophy of the left ventricular muscula-

ture; but inexorably the point is reached when under the stress of exercise the cardiac output can rise no further, and the coronary blood flow is at a fixed maximum even at rest.²⁵ This stage, then, characterized by severe left ventricular hypertension and normal cardiac output, may be termed "symptomatic but compensated."

C. *Decompensated*: Clinical evidence^{26,27} suggests that the symptomatic but compensated state can be maintained for approximately 2 years before the advent of irreversible myocardial failure. This is heralded by gradually rising left ventricular end-diastolic pressure, followed by a decrease in cardiac output and, finally, gross left ventricular dilatation where previously there had been only hypertrophy. As a consequence of the reduced flow the left ventricular systolic pressure falls, and, indeed, the hemodynamic features of the terminal, decompensated phase of aortic stenosis are low cardiac output, relatively little left ventricular systolic hypertension, elevated left ventricular end-diastolic pressure, a rather small pressure difference across the valve, and diminished cardiac work.

II. *Aortic Stenosis Complicated by Additional Lesions*.—A reduced cardiac output with only moderate left ventricular systolic hypertension and relatively small pressure difference across a tightly stenotic aortic valve may also be due to coexistent lesions, chiefly mitral stenosis, mitral regurgitation, and coronary artery disease.

Mitral stenosis combined with aortic stenosis is not uncommon. In this situation it is difficult to evaluate clinically the relative severity of the two lesions, but left heart catheterization allows accurate assessment of both valves. Mitral and aortic valvuloplasty during the same operation is feasible and usually well tolerated (Patients 14, 15, 16).⁹

Mitral regurgitation combined with aortic stenosis likewise presents a difficult problem of preoperative evaluation. Careful auscultation will usually suggest the diagnosis because of the presence of a characteristic apical pansystolic murmur distinct from the basal diamond-shaped ejection murmur of aortic stenosis. The radiologic finding of definite left atrial enlargement is the most reliable sign of a significant amount of mitral insufficiency. At left heart catheterization a diastolic pressure difference across the mitral valve, reduced cardiac output, and estimation of regurgitant flow from indicator dilution curves are of key help in evaluating the mitral lesion. Surgical correction of aortic stenosis is a beneficial form of treatment for mitral regurgitation, since it will favor systolic ejection through the enlarged aortic orifice rather than through the incompetent mitral valve and will lower the left ventricular systolic pressure, which is the *vis a tergo* for mitral regurgitation. This appeared to be the case in Patients 17 and 18.

Coronary disease frequently accompanies aortic stenosis, especially in the older age group. When coronary disease accompanies severe aortic stenosis, its presence may be suspected in the symptomatic but compensated patient from the finding of an otherwise unexplained reduction of cardiac output (Patient 19). Since angina and congestive failure are manifestations of both diseases, the relative severity of the two lesions is often impossible to assess by means other than left heart catheterization,^{19,28} which yields quantitative information in respect to the severity of aortic stenosis but not of coronary disease.

Aortic regurgitation is the single most difficult problem in the preoperative assessment of aortic stenosis. As in mitral disease, regurgitation aggravates and exaggerates the manifestations of stenosis. Since there is at present no practical method of measuring aortic regurgitant flow, the total blood flow across the valve during systole is unknown and orifice size cannot be calculated. The measurable forward cardiac output may be normal or low, and left ventricular systolic pressure may be greatly elevated in the face of a very high total systolic flow (aortic plus regurgitant flow) across a moderately stenotic and incompetent valve. Obviously, any calculation of orifice based on forward flow only would grossly underestimate the valve area in this situation. The Korner-Shillingford method for estimating regurgitant flow cannot differentiate between mitral and aortic incompetence and is at best semiquantitative. It has been applied rather extensively to the study of mitral insufficiency in this laboratory and by others, but its usefulness in the recognition of aortic regurgitation remains to be established. The evaluation of patients with combined aortic stenosis and regurgitation must therefore be based on a judicious assessment of all available clinical and catheterization data, in order to identify the hemodynamically predominant lesion and select appropriate therapy. It was on this basis that Patients 7-18 were considered to have "insignificant" aortic regurgitation and therefore to be suitable candidates for surgery for aortic stenosis, and yet postoperative findings were often disappointing (*vide infra*).

III. *Effects of Surgery.*—

A. *Aortic Valve Area:* In 11 patients the size of the aortic orifice was larger by 0.2 sq. cm. or more postoperatively. In 9 patients it was above the critical value of 0.7 sq. cm. Although the increase produced in the size of the valve was usually not great, it resulted in marked improvement, both clinically and objectively, because the left ventricular pressure falls as the *square* of the cross-sectional area of the valve increases, provided the flow is unchanged. No significant enlargement of the aortic orifice was accomplished in the other 8 patients. Brock²⁹ has suggested the possibility that acquired obstruction of the subaortic outflow tract due to hypertrophied left ventricular muscle may be responsible for some of these disappointing results, despite adequate relief of the valvular stenosis. By analogy with a course of events sometimes encountered in pulmonic stenosis,³⁰ one might speculate that gradual relief of residual subvalvular obstruction would occur as the hypertrophic muscle mass regressed following successful valvuloplasty. The two late postoperative studies in our series (Patient 13, 161 days; Patient 14, 432 days) had calculated valve areas of 0.9 and 0.7 sq. cm., giving little support to this thesis. Postmortem evidence indicates, rather, that the persistence of obstruction is at the valve itself, high-lighting the limitations of the surgical approach to these severely deformed, fused, and calcified structures.

B. *Cardiac Index:* The surgical procedure, when successful, did not tend to alter the cardiac index appreciably. The 11 patients with increased postoperative valve areas showed an average rise in cardiac index of 0.2 L./min./M.². In the 8 unimproved patients the flow decreased on an average of 0.9 L./min./M.². The difference between the means of these two groups is highly significant statistically ($P = <.01$).

C. *Pressures*: All patients experienced a reduction in left ventricular systolic pressure and in the pressure difference across the aortic valve during systole. The transvalvular pressure difference was completely eliminated only in Patient 15, concomitant with the production of significant regurgitation. The persistence of a pressure difference after surgery was also noted in all but one of Bailey's patients, studied by Smith and associates¹⁶; however, Gorlin³¹ and Abelmann and Taylor³² have studied 2 and 1 patients, respectively, selected and operated on by Dr. D. E. Harken in a similar manner, in whom the pressure difference across the aortic valve disappeared completely postoperatively, without the production of aortic regurgitation.

Relief of left ventricular hypertension is the primary goal of surgery for aortic stenosis. Whenever this was accomplished through the aegis of an enlarged aortic orifice, the surgical procedure was considered beneficial. Impressive falls in left ventricular systolic pressure and transaortic pressure difference were also seen in some of the patients with unimproved postoperative valve areas (Patients 6, 7, 8). In these the cause of the pressure drop was a marked postoperative reduction in cardiac output, usually attended by elevated left ventricular end-diastolic pressure. What would appear to be a gratifying result if only pressure measurements were made is thus revealed to carry the ominous implication of postoperative left ventricular failure, similar to the natural progression of the untreated disease.

The immediate effect of the operation on left ventricular function is perhaps best illustrated by the level of the left ventricular end-diastolic pressure, which was higher by more than 3 mm. Hg in the postoperative study in 8, unchanged or lower in 11, and above 10 mm. Hg in 14 patients. No correlation with the success or failure of enlarging the aortic orifice was found. The interpretation of such findings so soon after major surgery is not easy. Whether or not the left ventricular dysfunction is temporary or sustained is not revealed by this study.

IV. *Limitations of Surgery*.—Patient 15, as well as others not included in the present study, illustrate the potential danger of producing aortic regurgitation if too extensive a repair of aortic stenosis is attempted by present-day techniques. Even if aortic valvuloplasty is performed on postmortem specimens under direct vision, and valve action is studied by cinematography and pressure-flow measurements in an artificial perfusion system,^{23,33} it is difficult to obtain any semblance of normal cusp mobility in severe calcific aortic stenosis. Austen and associates³³ found that a distance approximately 2 mm. from the aortic wall was the limit to which the fused commissures could be divided with relative safety. Serial tests on the perfusion apparatus showed that more extensive freeing of the cusps toward their insertion into the aortic wall would lead to a rapidly rising incidence of disastrous regurgitation. It would appear that the area of 0.9 to 1.0 sq. cm. is the upper limit to which many, but not all, deformed calcific valves can be enlarged at present without running the risk of producing regurgitation. Nevertheless, a change in valve area from 0.5 to 1.0 sq. cm., while seemingly small, may make a very appreciable difference in left ventricular function and survival. At such a valve size, patients are asymptomatic short of violent exercise.

V. *Influence of Associated Lesions on Surgical Results.*—

Mitral Disease: All 5 patients with mitral disease, either stenosis or regurgitation, were among the 11 who showed postoperative enlargement of the aortic orifice. Mitral stenosis was adequately relieved by mitral valvuloplasty in Patients 14, 15, and 16, who underwent the combined operation, and the degree of mitral regurgitation in Patients 17 and 18 was reduced postoperatively, as judged by the Korner-Shillingford method, although the mitral valve was not operated upon. This phenomenon was accompanied by a rise in forward cardiac output in both patients and may well be attributable to preferential systolic ejection through the enlarged aortic orifice and lowering of the left ventricular systolic pressure.

Coronary Disease: The difficulties in establishing the relative severity of aortic stenosis and coronary artery disease when the two lesions coexist have been emphasized.²⁸ In Patient 19 severe coronary artery sclerosis was not recognized until the heart was exposed at the operating table; yet he underwent aortic valvuloplasty successfully. If aortic stenosis is severe and the patient symptomatic but compensated, surgery should be carried out, even though there is evidence of associated coronary disease.

Aortic Regurgitation: Six of the 8 patients who failed to show significant postoperative enlargement of the aortic orifice were from the group of 7 with preoperative "insignificant" aortic regurgitation as the only accompanying lesion (Patients 7, 8, 10, 11, 12, 13).

The term "insignificant" as applied to aortic regurgitation requires explanation. It implies that preoperatively only an aortic diastolic murmur of minor degree was present, without any of the peripheral stigmata of aortic insufficiency. Were this the sole lesion, it would indeed be insignificant. As pointed out earlier, however, the added transvalvular flow imposed by regurgitation aggravates the manifestations of stenosis in proportion to the amount regurgitated. If aortic stenosis is severe, any regurgitation thus becomes significant. Hence, the term "insignificant" regurgitation as applied to Patients 7-18 has been enclosed in quotation marks. The lack of hemodynamic improvement in 6 of these 12 patients may well indicate that the associated aortic regurgitation was by no means insignificant. It is our belief at this time that in the presence of severe aortic stenosis the assessment of otherwise insignificant regurgitation remains to be clarified.

The Korner-Shillingford analysis of indicator dilution curves failed to show an increase in regurgitant flow postoperatively in all but one of the patients in this group (Patient 10: 1+ regurgitation preoperatively, 2+ postoperatively). Nevertheless, it is quite possible and indeed likely that regurgitation persisted or was increased. In this event, surgically produced enlargement of the anatomic valve orifice may remain undetected by the method of calculation which takes into account only the forward (aortic) cardiac output. From the standpoint of body economy and cardiac load this would still not represent a beneficial surgical result. These observations suggest that even a degree of aortic regurgitation which is considered clinically "insignificant" may vitiate the efficacy of surgery for aortic stenosis as long as no technique is available for reducing the incompetence while relieving the stenosis.

VI. *Indications for Surgery for Aortic Stenosis.*—Although surgery for aortic stenosis cannot compare in efficacy with mitral valvuloplasty, it does appear to have a real place in therapy, but not, as others have advocated,¹⁶ in the presymptomatic phase of the disease. Until angina, syncope, or failure appear, the medical prognosis is excellent and much better than the surgical. With the advent of any of this triad of complications—especially left ventricular failure—the medical prognosis is poor (average life span about 2 years) while the surgical risk, in this clinic, is between 8 and 10 per cent.¹⁸ The follow-up of these patients is too short to render an accurate prognosis after surgery. It will, in time, be described elsewhere.²⁴

If aortic stenosis is severe and the patient symptomatic, surgery should be carried out even in the presence of mitral stenosis, mitral regurgitation, or coronary disease. Associated aortic regurgitation, even of clinically minor degree, frequently appears to be unrelieved and possibly even enhanced by the present surgical approach to aortic stenosis. Operation in most such patients should probably be withheld until evidence accumulates that regurgitation can be dealt with successfully.

This report does not include any patients in the terminal, decompensated phase of aortic stenosis, characterized by low cardiac output, relatively low left ventricular systolic pressure, small transvalvular systolic pressure difference, and gross left ventricular dilatation. Experience with such cases to date indicates a well-nigh prohibitive surgical risk. Although this risk must be balanced against a hopeless medical prognosis, operation cannot be advocated for such patients, since their circulatory status has become one of advanced myocardial failure and practically no mechanical embarrassment from the severe stenosis. It is the latter and not the former which surgery aims to relieve.

SUMMARY

1. Nineteen patients with severe aortic stenosis have been studied by left heart catheterization before and after transaortic valvuloplasty.
2. The cardiac index was normal in patients with pure aortic stenosis but tended to be reduced in the presence of associated aortic regurgitation, mitral or coronary disease.
3. Severe aortic stenosis, as it progresses, may become associated with a reduced cardiac output and, therefore, a small systolic mean pressure difference across the aortic valve.
4. There was a small but significant postoperative increase in calculated aortic valve area in 11 patients, associated with a marked fall of left ventricular systolic pressure, transvalvular pressure difference, and left ventricular work, while cardiac output remained unchanged. A residual pressure difference across the aortic valve persisted in all but one patient, who developed severe regurgitation.
5. Eight patients showed no change in valve area. The left ventricular systolic pressure and transvalvular pressure difference in these was also decreased postoperatively, but this was found to be the result of reduced cardiac output.
6. Associated mitral stenosis, mitral regurgitation, or coronary disease did not preclude successful surgery for aortic stenosis.

7. Six of the 8 operative failures occurred among 7 patients with clinically "insignificant" preoperative aortic regurgitation as the only complicating lesion. Operation in this group either did not relieve the stenosis or increased the regurgitation in proportion to the relief of stenosis so that measurable benefit was not observed.

8. The meaning of the term "insignificant" as it pertains to pure aortic regurgitation and to regurgitation associated with severe aortic stenosis is discussed.

9. Indications and contraindications for surgery for aortic stenosis are discussed.

REFERENCES

1. Bailey, C. P., Glover, R. P., O'Neill, T. J. E., and Redondo-Ramirez, H. P.: *J. Thoracic Surg.* **20**:156, 1950.
2. Bailey, C. P., Bolton, H. E., Jamison, W. L., and Larzelere, H. B.: *J. Internat. Coll. Surgeons* **20**:393, 1953.
3. Sarnoff, S. J., Donovan, T. J., and Case, R. B.: *Circulation* **11**:564, 1955.
4. Brock, R.: *Brit. M. J.* **1**:1019, 1957.
5. Bailey, C. P., Bolton, H. E., Nichols, H. P., Jamison, W. L., and Litwak, R. S.: *J. Thoracic Surg.* **31**:375, 1956.
6. Bailey, C. P., Bolton, H. E., Jamison, W. L., and Nichols, H. P.: *Circulation* **9**:22, 1954.
7. Bailey, C. P., Redondo-Ramirez, H. P., and Larzelere, H. B.: *J.A.M.A.* **150**:1647, 1952.
8. Larzelere, H. B., and Bailey, C. P.: *J. Thoracic Surg.* **26**:31, 1953.
9. Bailey, C. P., and Likoff, W.: *A.M.A. Arch. Int. Med.* **99**:859, 1957.
10. Baker, C. G., and Campbell, M.: *Lancet* **270**:171, 1956.
11. Uricchio, J. F., Litwak, R., Denton, C., Goldberg, H., and Likoff, W.: *Ann. Int. Med.* **44**:844, 1956.
12. Litwak, R. S., Uricchio, J. F., and Likoff, W.: *New England J. Med.* **254**:781, 1956.
13. Wood, P.: *Am. J. Cardiol.* **1**:553, 1958.
14. Mueller, W. H., Jr., Kattus, A. A., Dammann, J. F., and Smith, R. T.: *J. Thoracic Surg.* **28**:516, 1954.
15. Bakst, A. A., Cohen, C., and Loewe, L.: *AM. HEART J.* **53**:193, 1957.
16. Smith, R. C., Bailey, C. P., and Goldberg, H.: *J. Thoracic Surg.* **34**:815, 1957.
17. Harken, D. E., Black, H., Taylor, W. J., Thrower, W. B., and Soroff, H. S.: *New England J. Med.* (In Press.)
18. Harken, D. E., Black, H., Taylor, W. J., Thrower, W. B., and Soroff, H. S.: *J. Thoracic Surg.* **36**:759, 1958.
19. Dexter, L., Harken, D. E., Cobb, L. A., Novack, P., Schlant, R. C., Phinney, A. O., Jr., and Haynes, F. W.: *A.M.A. Arch. Int. Med.* **101**:254, 1958.
20. Kinsman, J. M., Moore, J. W., and Hamilton, W. F.: *Am. J. Physiol.* **89**:322, 1929.
21. Gorlin, R., and Gorlin, S. G.: *AM. HEART J.* **41**:1, 1951.
22. Novack, P., and Schlant, R. C.: *In Methods in Medical Research*, Vol. 7, Chicago, 1958, Year Book Publishers, Inc., p. 76.
23. McMillan, I. K. R.: *Brit. Heart J.* **17**:56, 1955.
24. Gorlin, R., McMillan, I. K. R., Reed, W. E., Mathews, E. B., and Daley, R.: *Am. J. Med.* **18**:855, 1955.
25. Gorlin, R., Brachfeld, N., MacLeod, C., and Bopp, P.: *Circulation* **19**:705, 1959.
26. Mitchell, A. M., Sackett, C. H., Hunzicker, W. J., and Levine, S. A.: *AM. HEART J.* **48**:684, 1954.
27. Bergeron, J., Abelman, W. H., Vazquez-Milan, H., and Ellis, L. B.: *A.M.A. Arch. Int. Med.* **94**:911, 1954.
28. Hancock, E. W., Madison, W. M., Jr., Proctor, M. H., Abelman, W. H., and Starkey, G. W. B.: *New England J. Med.* **258**:305, 1958.
29. Brock, R.: *Guy's Hosp. Rep.* **106**:221, 1957.
30. Engle, M. A., Holswade, G. R., Goldberg, H. P., Lukas, D. S., and Glenn, F.: *Circulation* **17**:862, 1958.
31. Gorlin, R.: Personal Communication.
32. Abelman, W. H., and Taylor, W. J.: Personal Communication.
33. Austen, W. G., Shaw, R. S., Scannell, J. G., and Thurlbeck, W. M.: *J. Thoracic Surg.* **36**:571, 1958.
34. Ellis, L. B., Harken, D. E., et al.: (To be published.)

The Electrocardiogram and Ventricular Gradient in Atrial Septal Defect

George E. Burch, M.D., and Nicholas DePasquale, M.D., New Orleans, La.

With improvement in the diagnosis of congenital cardiac defects the electrocardiographic patterns associated with specific defects are better recognized. A number of reports have appeared which indicate a fairly characteristic electrocardiographic pattern in association with atrial septal defect.¹⁻⁶ This report is concerned with a study of 100 patients with uncomplicated atrial septal defects in whom the diagnosis was established by catheterization, surgery, or autopsy. These studies show the value of the electrocardiogram in the clinical diagnosis and evaluation of the patient with atrial septal defect.

METHODS AND MATERIALS

One hundred patients from the Charity Hospital and Tulane University Medical School constituted the clinical material for this study. These patients had proved atrial septal defects and had had one or more routine electrocardiograms recorded. The diagnosis of uncomplicated atrial septal defect was made by cardiac catheterization in 82 patients, by surgery in 13 patients, and by autopsy in 5 patients. The catheterization criteria for diagnosis of an atrial septal defect

TABLE I. AGE, SEX, AND RACE INCIDENCE IN 100 PATIENTS WITH CONGENITAL ATRIAL SEPTAL DEFECT

AGE (YR.)	SECUNDUM				PRIMUM			
	WHITE	NEGRO	MALE	FEMALE	WHITE	NEGRO	MALE	FEMALE
0-5	12	7	8	11	3	1	1	3
6-10	13	4	8	9	—	—	—	—
11-15	3	3	—	6	1	—	—	1
16-20	7	5	3	9	2	1	—	3
21-30	8	2	2	8	1	—	—	1
31-40	12	4	5	11	1	—	—	1
41-50	4	—	2	2	—	—	—	—
51-65	2	4	3	3	—	—	—	—
Totals	61	29	31	59	8	2	1	9

From the Department of Medicine, Tulane University School of Medicine, and Charity Hospital of Louisiana, New Orleans, La.

This work was supported by the U.S. Public Health Service, the Upjohn Company, and the Thibodeaux Research Foundation.

Received for publication April 2, 1959.

were: (1) an increase in oxygen saturation of at least 2 volumes per cent between the superior vena cava and the right atrium, (2) passage of the catheter through the defect, and (3) dye dilution curves when available. The electrocardiograms selected for analysis were recorded within two to three days of cardiac catheterization.

There were no findings compatible with any other defect except in 3 patients in whom there was anomalous venous return to the right atrium, and in 3 other patients, hypertrophy of the crista supraventricularis produced slight but definite functional infundibular pulmonary stenosis.

The age of the patients varied from 1 month to 62 years. Sixty-eight of the patients were females and 32 were males. Sixty-nine were white and 31 were Negro (Table I). Ninety patients had proved septum secundum defects, and 6 had proved septum primum defects (4 at surgery and 2 at autopsy). Four patients had clinical and catheterization data which were compatible with septum primum defect because of an apical systolic murmur of the type usually associated with such a defect, and because of repeated passage of the catheter from the right atrium into the left ventricle in a manner compatible with a septum primum defect.

Conventional clinical, electrocardiographic, and cardiac catheterization data were employed in these investigations, as were other routine and special studies and analyses.

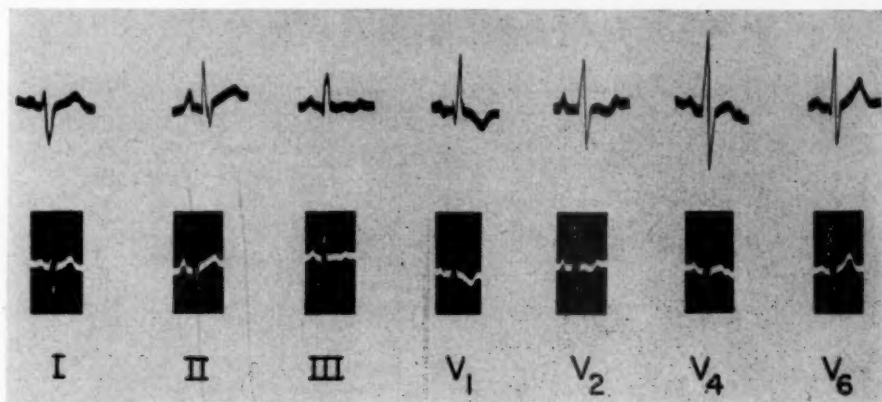


Fig. 1.—Typical electrocardiogram of septum secundum defect.

RESULTS

The electrocardiographic patterns of the septum primum and the septum secundum defects were characteristically different, so different in these 100 patients that it was easy to separate the electrocardiograms of the patients with the septum primum defects from those of the patients with the septum secundum defects.

The Electrocardiogram of the Septum Secundum Defect.—A typical electrocardiogram of a patient with a septum secundum defect is shown in Fig. 1. All but one patient with this defect had electrocardiograms with this general configuration. The typical electrocardiogram consisted of a prominent S wave in Lead I. This S wave was prominent because it was either wide or of large magnitude, or both. The QRS complex was mainly positive or had an R wave in Leads II and III, so that the mean electrical axis of the QRS complex was usually located in the fifth sextant of the triaxial reference system of the frontal plane (Fig. 2). The S wave in Lead V₁ was usually small, to almost an absence of an S wave, and there was a large R or R' wave or at least a definite R' wave. The S wave in Leads V₅ and V₆ was prominent because of either its relatively long

duration or great magnitude, or both; the R wave in Leads V_5 and V_6 was relatively low in magnitude in comparison with the S wave. There were no diagnostically characteristic changes in the T waves. Tables II and III summarize the vectorial characteristics of \hat{A}_{QRS} , \hat{A}_T , and \hat{G} for the 90 patients with septum secundum defect. The \hat{A}_{QRS} tended to be vertically oriented in the frontal projection, was of average magnitude, and usually was located to the right of \hat{G} (79 of 90 patients), and of course to the right of \hat{A}_T also. The angle between \hat{A}_{QRS} and \hat{G} was abnormally large in 22 of the 90 patients, and that between the \hat{A}_T and \hat{G} was abnormal in 29 patients. Forty of the 90 patients had an abnormally wide angle between either \hat{A}_{QRS} and \hat{G} or \hat{A}_T and \hat{G} , or between both (Table IV).

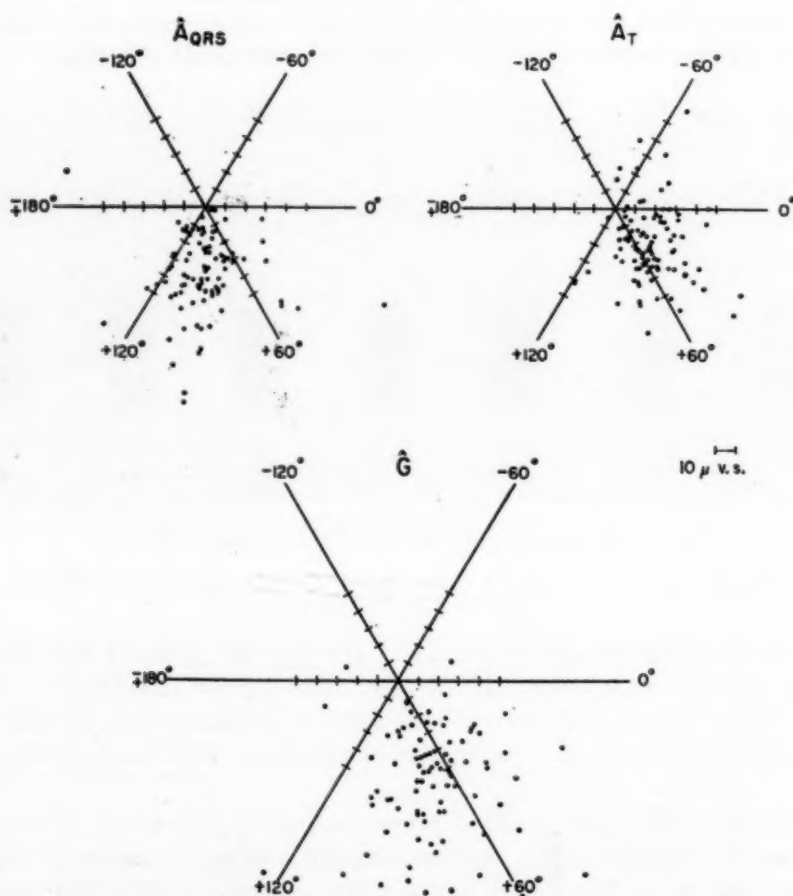


Fig. 2.— \hat{A}_{QRS} , \hat{A}_T , and \hat{G} of ninety septum secundum defects.

Because the electrocardiogram is considered to indicate incomplete or complete right bundle branch block in atrial septal defect, the electrocardiograms from our patients were found to be readily grouped into four additional subgroups.

1. The electrocardiograms of 23 of the 90 patients (26.5 per cent) had the generally accepted electrocardiographic criteria of *complete* right bundle branch

block, in that the duration of the QRS complex exceeded 0.12 second for a cardiac rate in the seventies or a comparably long duration for other rates (Fig. 3, D).

2. Twenty-nine of the 90 patients (32.2 per cent) had a pattern usually considered to indicate *incomplete* right bundle branch block (Fig. 3,C). This group differed from the aforementioned group in that the QRS complex did not exceed 0.12 second, but did exceed 0.10 second for cardiac rates in the seventies or was of comparable duration for other rates.

3. Thirty-one of the 90 patients (34.4 per cent) had the electrocardiographic pattern of incomplete right bundle branch block, except that the duration of the QRS complex was within normal limits (Fig. 3,B).

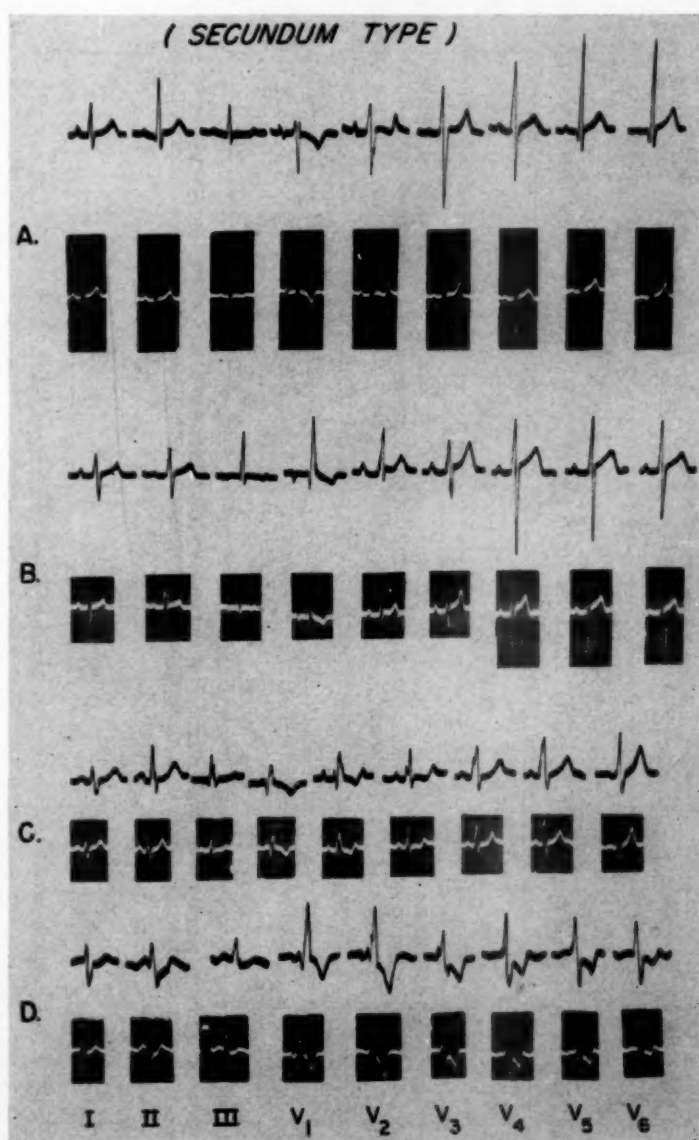


Fig. 3.—Four electrocardiographic patterns in septum secundum defects.

TABLE II. MEANS AND EXTREMES OF \dot{A}_{QRS} , \dot{A}_T , AND \dot{G} IN 10 PATIENTS WITH SEPTUM PRIMUM DEFECTS AND IN 90 WITH SEPTUM SECUNDUM DEFECTS

	SECUNDUM				PRIMUM			
	MEAN POSITION (DEGREES)	RANGE (DEGREES)	MEAN MAGNITUDE (μ V.S.)	RANGE (μ V.S.)	MEAN POSITION (DEGREES)	RANGE (DEGREES)	MEAN MAGNITUDE (μ V.S.)	RANGE (μ V.S.)
\dot{A}_{QRS}	93	12, +194*	38	4, 102	-34	-84, 0	26	64, 1
\dot{A}_T	41	-85, +120	32	4, 79	36	80, -26	33	80, 9
\dot{G}	71	-20, +194	60	12, 136	5	32, -49	43	88, 10



*For convenience in evaluating mean direction of the vectors and other parameters when the magnitude of the angle indicating direction of the vector was located in the third sextant, the value of the angle was indicated as having been obtained by clockwise rotation beyond +180° or +194° in this instance rather than -166°.



TABLE III. RELATIONS OF ELECTROCARDIOGRAPHIC PARAMETERS TO AGE IN 90 PATIENTS WITH SEPTUM SECUNDUM DEFECTS AND IN 10 PATIENTS WITH SEPTUM PRIMUM DEFECTS—(MEAN VALUES ARE SHOWN)

AGE (YR.)	\hat{A}_{QRS}		\hat{A}_T		\hat{C}		QRS	P-R	RV	SHUNT
	MEAN POSITION (DEGREES)	MEAN MAGNITUDE (μ V.S.)	MEAN POSITION (DEGREES)	MEAN MAGNITUDE (μ V.S.)	MEAN POSITION (DEGREES)	MEAN MAGNITUDE (μ V.S.)	DURATION (SEC.)	INTERVAL (SEC.)	SYSTOLIC PRESSURE (MM. HG)	PBF — SBF
<i>Secundum</i>										
0-5	99	30	57	33	74	54	0.078	0.147	49	3.6
6-10	89	36	34	27	70	50	0.085	0.167	45	1.8
11-15	80	48	37	38	52	76	0.088	0.160	37	1.6
16-20	89	48	31	36	65	65	0.096	0.190	53	2.3
21-30	100	30	23	34	62	54	0.101	0.181	33	3.0
31-40	83	47	43	33	66	56	0.107	0.172	37	2.4
41-50	107	62	43	31	97	81	0.125	0.160	51	3.4
51-65	94	26	47	20	75	59	0.110	0.175	49	3.2
<i>Primum</i>										
0-32	-34	26	36	33	5	43	0.097	0.184	—	—

4. Seven of the 90 patients (7.7 per cent) had an electrocardiographic pattern which was normal or only slightly suggestive of incomplete right bundle branch block, with a QRS complex of normal duration (Fig. 3,4). The tracing of one of these patients had no evidence suggestive of the pattern described above for atrial septal defect.

TABLE IV. THE DISTRIBUTION IN NUMBER OF PATIENTS OF THE MAGNITUDE OF THE ANGLE BETWEEN \hat{A}_{QRS} AND \hat{C} , AND \hat{A}_T AND \hat{C}

Magnitude of angle									
Position of \hat{A}_{QRS} relative to \hat{C}		SECUNDUM				PRIMUM			
		Patients (Total)	0°-35°	36°-70°	> 70°	Patients (Total)	0°-35°	36°-70°	> 70°
Right:		79	59	18	2	0	--	--	--
Left:		11	9	2	0	10	4	6	--

Position of \hat{A}_T relative to \hat{C}									
Right:		11	9	1	1	10	7	2	1
Left:		79	52	18	9	0	--	--	--

The Electrocardiogram of Septum Primum Defect.—Septum primum defect is considered, in this presentation, to include the mild and severe defects of the basal segment of the ventricular septum at the atrioventricular region, and it therefore includes persistent ostium atrioventricularis communis, with or without incompetence of the atrioventricular valves.

The routine electrocardiogram in this type of defect had essentially the same general pattern as that described above for the atrial septum secundum defect, except that the standard leads showed a left axis deviation of the QRS complex. Fig. 4 shows a typical electrocardiogram of septum primum defect. The vector of the \hat{A}_{QRS} of the 10 patients studied was located in the first and second sextants of the triaxial reference system. The vectors of \hat{A}_T and \hat{C} were deviated to the left but not so much so as the vector of \hat{A}_{QRS} (Fig. 5, and Tables II and III).

The *T waves* were not significantly altered in most of the patients. Alterations due to congestive heart failure, digitalis, and myocardial disease when present were not characteristic of atrial septal defect. As indicated by the tables and illustrations (Figs. 5, 6, and Tables II, III), \hat{A}_T was not greatly deviated from the normal nor was the \hat{A}_T of the septum secundum defects significantly different from those of the septum primum defects (Figs. 2, 5, 6).

The *P* wave was modified very little in the standard leads of most patients. It was prominent in Leads II and III in 13 per cent of the patients with secundum defects, and in 30 per cent of the patients with primum defects. In Lead V_1 a diphasic *P* wave of the type considered fairly characteristic of enlargement of the right atrium was present in 50 per cent of the patients with secundum defect, and in 50 per cent of the patients with primum defect (Table V).

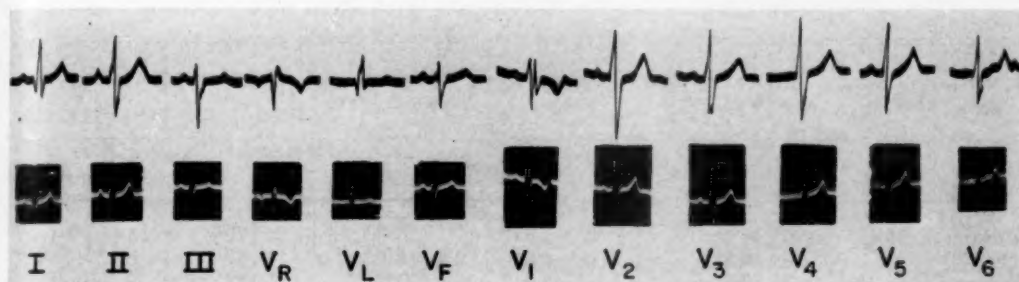


Fig. 4.—Typical electrocardiogram of septum primum defect.

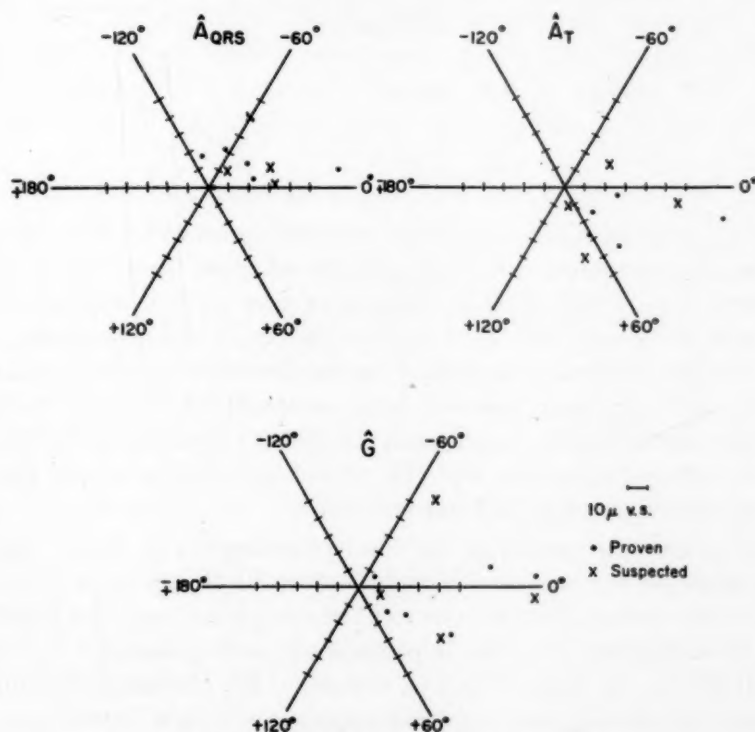


Fig. 5.— \hat{A}_{QRS} , \hat{A}_T , and \hat{G} of ten septum primum defects.

The *P-R* interval was prolonged in 19 per cent of the patients with secundum defect, and in 40 per cent of the patients with primum defect, or 21 (21 per cent) of the 100 patients with atrial septal defects.

A definite *Q* wave in precordial leads recorded from the right side of the transition zone, and considered as an indication of enlargement of the right atrium

by Sodi-Pallares,⁷ was noted in 33 per cent of the patients with septum secundum defect, and in 20 per cent of the patients with septum primum defect (Table V).

Auricular fibrillation was present in 4 of the patients with secundum defect, and in none of the patients with primum defect.

TABLE V. THE INCIDENCE OF ELECTROCARDIOGRAPHIC EVIDENCE OF MYOCARDIAL DISEASE, AND P-WAVE ABNORMALITIES AND Q WAVE IN LEADS V₁ AND/OR V₂ IN THE 90 PATIENTS WITH SECUNDUM DEFECTS AND THE 10 PATIENTS WITH PRIMUM DEFECTS

ECG PATTERN	T-WAVE ABNORMALITY	HEIGHT OF P-II (MV.)	PER CENT ABOVE 2.3 MV.	DIPHASIC P IN V ₁	Q IN V ₁ OR V ₂
<i>Secundum</i>					
"Complete Block"	9 (39%)	1.7 (0.2-3.5)	3 (15%)	14 (70%)	13 (56%)
"Delay"	3 (10.3%)	1.6 (0.1-4.6)	5 (18%)	14 (50%)	8 (27%)
Narrow QRS	3 (10%)	1.7 (0.5-4.0)	4 (13%)	15 (48%)	9 (30%)
Normal	0	1.0 (0.2-2.0)	0	2 (28%)	0
Totals	15 (16%)	1.5 (0.1-4.6)	12 (13.3%)	45 (50%)	30 (33.3%)
<i>Primum</i>					
	6 (60%)	1.9 (0.8-4.0)	3 (30%)	5 (50%)	2 (20%)

DISCUSSION

In cases of atrial septal defect the electrocardiogram was fairly characteristic, that of the septum secundum defect being quite different from that of the septum primum defect (Figs. 1 and 4). The differences were so definite that the electrocardiogram was of considerable value in the differential diagnosis of the two types of defects. The mechanisms responsible for the two electrocardiographic patterns are unknown, and although observers have attempted to explain them, the explanations have been mainly conjectural. It is most likely that the patterns are related to the relative amounts, and the spatial orientation within the body, of the muscle masses of the right and left ventricles.

Another interesting aspect of the electrocardiogram in atrial septal defect is the mechanism of the so-called bundle branch block patterns. As indicated previously,⁸⁻¹⁰ the rather arbitrary electrocardiographic criteria for bundle branch block need re-evaluation, and this is particularly well illustrated in instances of atrial septal defect. As pointed out by others,⁶⁻⁸ the electrocardiogram in cases of atrial septal defect may have a pattern suggestive of right bundle branch block, but apparently the mechanism for the pattern is not interference with conduction of the impulse through the right bundle branch. The tracings of the 100 patients included in this study add further support to this concept. For example, the QRS pattern of right bundle branch block can exist in atrial septal defect, with the duration of the QRS complex varying from normal to over 0.12 second (Fig. 3, C and D). All patients of this series whose QRS complex exceeded 0.12 second were adults who were in their late third decade or older, and who thus satisfied

the arbitrary electrocardiographic criteria of complete right bundle branch block. Since the longest QRS intervals were found in the older patients, the longer the atrial septal defects existed the greater was the right ventricular hypertrophy, especially of the crista supraventricularis. The thicker and the greater the mass of muscle forming the crista, the longer the time required to complete depolarization and the greater the duration of the QRS. In no instance in this series was the QRS complex over 0.12 second in an infant or child. It would be expected that the rate of development of myocardial hypertrophy would be directly related to the amount of work performed by the muscle. There was a direct relationship of duration of the QRS complex to the age of the patient and, therefore, duration of the defect (Fig. 7, and Table III).

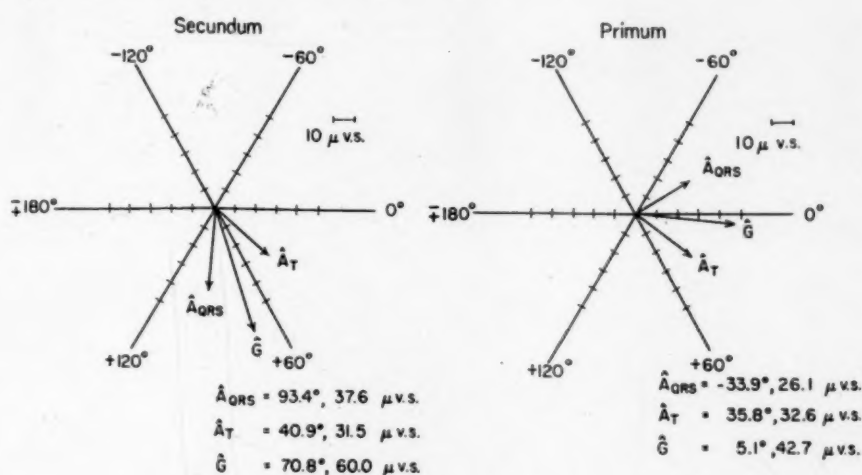


Fig. 6.—Mean \hat{A}_{QRS} , \hat{A}_T , and \hat{G} in atrial septal defects.

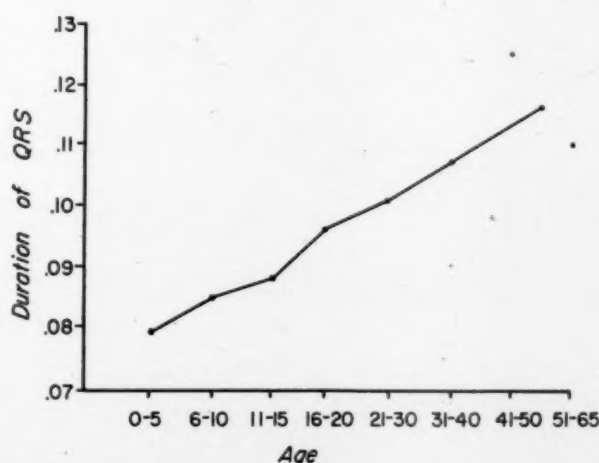


Fig. 7.—Relationship of QRS interval to age in ninety cases of septum secundum defect.

The pattern of right ventricular hypertrophy superimposed upon the pattern of hypertrophy of the crista supraventricularis was found to occur in the electrocardiograms of patients with diffuse hypertrophy of the right ventricle. This

was observed, for example, in patients with functional stenosis of the infundibulum (Fig. 8). These details need further clarification by careful gross and microscopic pathologic studies.

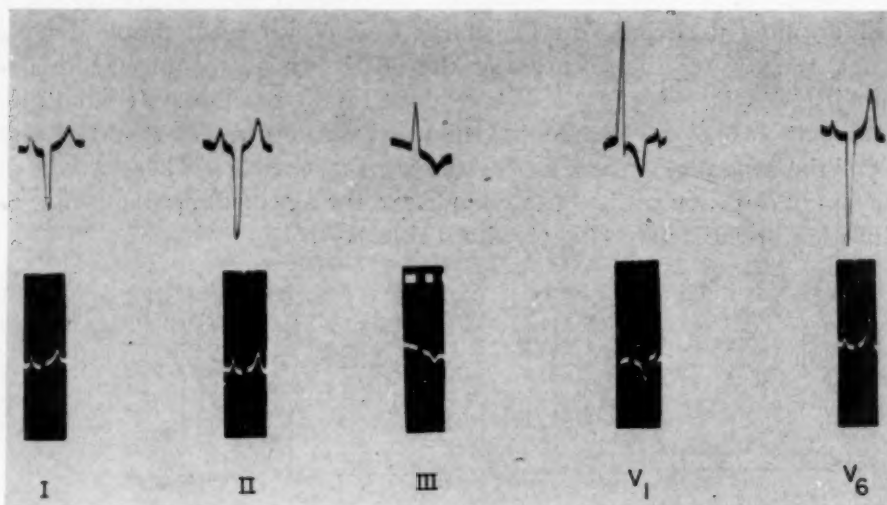


Fig. 8.—Electrocardiogram in a patient with interatrial septal defect and functional stenosis of the infundibulum.

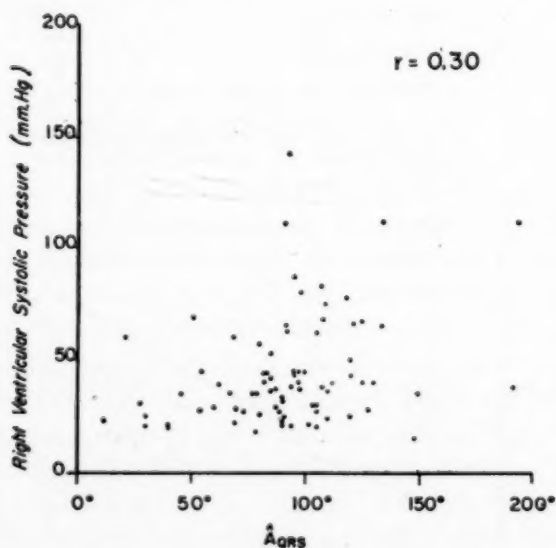


Fig. 9.—Relationship of electrical position of \hat{A}_{QRS} to right ventricular systolic pressure.

When the electrocardiograms of 78 patients with septum secundum defects were studied for the relationship of the electrical position of the \hat{A}_{QRS} to the systolic blood pressure in the right ventricle, the correlation coefficient was only 0.30 (Fig. 9). The relationship between magnitude of the atrial shunt and the position of the \hat{A}_{QRS} in 76 patients had a correlation coefficient of 0.20 (Fig. 10).

The reasons for the lack of relationship between these parameters is not known. It must be due in part to the inaccuracies of the measurements, especially of the size of the atrial shunt, as well as the failure of a single measurement on a catheterization table for a short moment of a person's life to represent the average

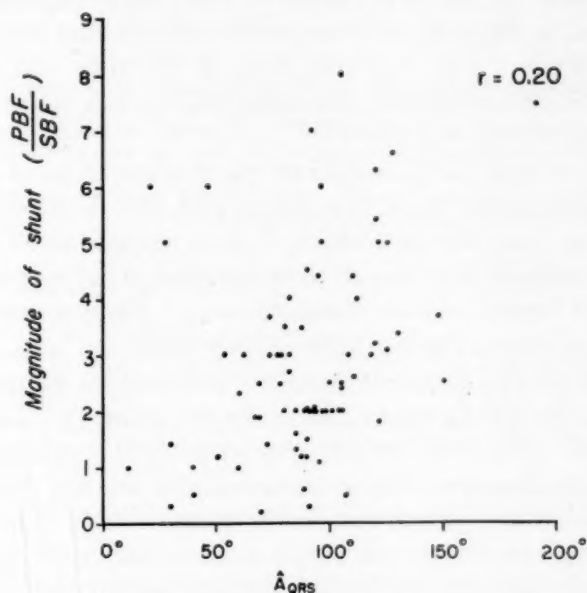


Fig. 10.—Relationship of the size of the atrial shunt to electrical position of \hat{A}_{QRS} .

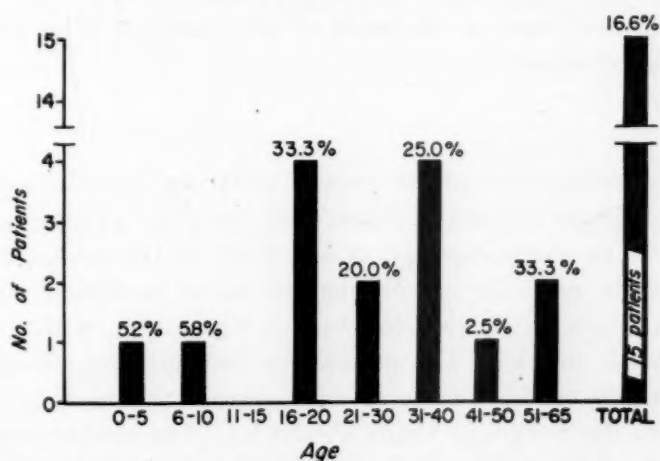


Fig. 11.—Age distribution of patients with septum secundum defect with ECG evidence of myocardial disease.

state throughout his life. It would be expected that the work (intrachamber pressure-volume-time course curves) of a cardiac chamber would be directly related to the amount of its muscle mass, which in turn would be related to the magnitude and spatial orientation of the \hat{A}_{QRS} .

The \hat{A}_{QRS} and ventricular gradient \hat{G} tended to be vertical or deviated to the right in the frontal plane projection in the patients with septum secundum

defect, and horizontal or deviated to the left in patients with septum primum defect (Fig. 6). \hat{A}_T was not significantly different in magnitude or direction in the frontal plane projection in most of the patients with the two types of defects. Therefore, the ventricular gradient was different in the two types of defects mainly because of differences in the time course of ventricular depolarization. \hat{G} was oriented to the left of \hat{A}_{QRS} in most secundum defects, and to the right of \hat{A}_{QRS} in all primum defects. This was true because the time course of ventricular repolarization remained essentially the same for the two types of atrial defects. The data are summarized in Table IV.

It is difficult to explain the failure of the P wave to be of great magnitude or duration in the standard leads in patients with this defect in whom the right atrium is large. In Lead V_1 the diphasic P wave of right atrial enlargement was common in these patients and proved to be the most reliable electrocardiographic sign of right atrial hypertrophy and enlargement. The presence of a Q wave in Lead V_1 was not always a finding in these patients.

On the basis of all electrocardiographic parameters, including the relative positions of \hat{A}_{QRS} , \hat{A}_T , and \hat{G} , 54 per cent of the 90 patients with septum secundum defect, and 80 per cent of the 10 patients with septum primum defect had an abnormal electrocardiogram. These abnormalities do not necessarily indicate disease, degeneration, or malfunction of the myocardium. For example, hypertrophy of the crista supraventricularis with an associated prolonged QRS duration does not necessarily indicate myocardial disease, but an alteration of the heart such as any heart with a normal myocardium would be expected to develop under such circumstances. Only 16 per cent of the patients had T-wave changes which were considered abnormal on the basis of configuration (Fig. 11), while in 44 per cent, \hat{G} was abnormal in position.

SUMMARY

The electrocardiograms in 100 proved instances of atrial septal defect (90 patients with septum secundum defect and 10 with septum primum defect) were studied. The electrocardiogram was fairly characteristic in atrial septal defect, sufficiently so to be of considerable value in clinical diagnosis. The tracings had a prominent S wave in Leads I, V_5 , and V_6 , with a prominent R' wave in Leads V_1 and V_2 . The prominence included large magnitude and/or duration, especially when considered with respect to the R wave in Leads I, V_5 , and V_6 , and the S wave in Leads V_1 and V_2 . The electrocardiograms of the septum primum defects differed significantly in a readily recognizable fashion from those of the septum secundum defects, in that the former also manifested left axis deviation of the QRS or \hat{A}_{QRS} , while in the latter the axis was shifted toward the right. This was evident from an S wave of considerable magnitude in Leads II and III. Not one of the 90 patients with septum secundum defect manifested left axis deviation of the QRS complex or \hat{A}_{QRS} .

The P wave was not particularly altered in the electrocardiogram, except in Lead V_1 , in spite of right atrial enlargement in atrial septal defect.

These studies show again the unreliability of the arbitrary electrocardiographic criteria of right bundle branch block. The 100 sets of tracings also indicate the value of the electrocardiogram in differentiating hypertrophy of the crista supraventricularis from that of the entire right ventricle.

REFERENCES

1. Vizcaino, M., Vaquero, M., and Pellón, R.: Comunicación interauricular, estudio de 20 Casos. III. Congreso Cardiológico Interamericano, Chicago, Ill., 1948.
2. Routier, D., and Heim de Balsac, R.: Six observations cliniques de malformations congénitales cardiaques du type dit "communication interauriculaire," *Bul. Soc. Belge Cardiol.*, Seance du 15 Janvier, 1939.
3. Limon Lason, R., Esclavissat, M., Puech, P., De La Cruz, M. V., Rubio, V., Bouchard, F., and Soní, J.: El cateterismo intracardiaco; la comunicación interauricular. Correlación de los hallazgos hemodinámicos con los datos embriológicos, clínicos, radiológicos y electrocardiográficos en 50 casos, *Arch. Inst. cardiol. México* **23**:279, 1953.
4. Barber, J. M., Magidson, O., and Wood, P.: Atrial Septal Defect With Special Reference to the Electrocardiogram, the Pulmonary Artery Pressure and the Second Heart Sound, *Brit. M. J.* **12**:277, 1950.
5. Toscano Barboza, E., Brandenburg, R. O., and Swan, H. J. C.: Atrial Septal Defect: The Electrocardiogram and Its Hemodynamic Correlation in 100 Proved Cases, *Am. J. Cardiol.* **2**:698, 1958.
6. Toscano Barboza, E., Brandenburg, R. O., and Burchell, H. B.: Electrocardiographic Studies of Cases With Intracardiac Malformations of the Atrioventricular Canal, *Proc. Staff Meet. Mayo Clinic*, **31**:513, 1956.
7. Sodi-Pallares, D., Thomsen, P., Soberon, J., Fishleder, B. L., Estandia, A., and Barbato, E.: El electrocardiograma intracavtario humano, Mexico, Instituto Nacional de Cardiologia **110**, 1948.
8. Martins de Oliveira, J., and Zimmerman, H. A.: The Electrocardiogram in Interatrial Septal Defects and Its Correlation With Hemodynamics, *AM. HEART J.* **55**:369, 1958.
9. Walker, W. J., Mattingly, T. W., Pollock, B. E., Carmichael, D. B., Inmon, T. W., and Forrester, R. H.: Electrocardiographic and Hemodynamic Correlation in Atrial Septal Defect, *AM. HEART J.* **52**:547, 1956.
10. Cabrera, E., and Monroy, J. R.: Systolic and Diastolic Loading of the Heart, II, Electrocardiographic Data, *AM. HEART J.* **43**:669, 1952.

Experimental and Laboratory Reports

Changes in Cardiac Output, Stroke Volume, and Central Venous Pressure Induced by Atropine in Man

J. Norman Berry, M.D., Howard K. Thompson, Jr., M.D., D. Edmond Miller, M.D., and Henry D. McIntosh, M.D., Durham, N. C.*

INTRODUCTION

Atropine is frequently used in the cardiovascular laboratory as a simple and effective means of increasing the heart rate. Despite previous studies^{1,5} it is not generally appreciated that the intravenous injection of sufficient atropine to produce tachycardia (1 mg. or more) may also produce an increase in cardiac output and a fall in central venous pressure. The genesis of these changes is unknown.

The present study was designed to investigate the nature of the hemodynamic changes associated with atropinization of normal recumbent subjects. The results confirm the previous reports of an increase in cardiac output and a fall in central venous pressure,³⁻⁵ and, in addition, demonstrate that the maximum increase in cardiac output occurs within 3 minutes after the intravenous administration of atropine. There is no change in stroke volume during this early period; however, following this 3-minute interval there is a relative decline in cardiac output but no change in heart rate, resulting in a significant fall in stroke volume. In order to study the mechanisms responsible for these changes, the effects of certain maneuvers intended to increase venous return were studied before and after the administration of atropine.

From the Department of Medicine, Duke University Medical Center, Durham, N. C.

This investigation was supported in part by Research Grant No. H-3343 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service, and grants from the American Heart Association and the North Carolina Heart Association.

Preliminary abstract of this article was published in *Clinical Research* 6:216, 1958.

Received for publication April 20, 1959.

*U. S. Public Health Service Research Fellow, 1957-58.

MATERIALS AND METHODS

Twenty male university students, a female patient with essential hypertension, and a male patient with a peptic ulcer were studied. The vital statistics of these 22 subjects are recorded in Table I. All observations were made with the subjects in the postabsorptive state and recumbent, except when specifically indicated otherwise. Two subjects were studied twice (E.C. and J.B.).

A No. 6 or No. 7 calibrated cardiac catheter was passed from an antecubital vein into the superior vena cava just proximal to the right atrium, and a No. 18 indwelling Cournand needle was inserted into a brachial artery for the collection of blood and measurement of pressure. In most subjects a No. 20 indwelling needle was inserted into a radial artery to permit uninterrupted pressure recording during the arterial sampling procedures. Arterial and central venous pressures were recorded on a multichannel photographic Electronics for Medicine research recorder or a Sanborn Poly-Viso direct-writing recorder via Statham P23D or P23G pressure transducers. The base line for the central venous pressure was established 5 cm. below the sternal angle. Mean pressures were obtained by electrical integration over a period including at least two respiratory cycles. Heart rate was determined from a continuous electrocardiographic tracing. Cardiac output, mean circulation time, and "central blood volume" were calculated from T-1824 dye dilution curves according to the method of Hamilton.⁶ In all instances the existence of a steady state was verified by constancy of pulse rate, blood pressure, and mean venous pressure before the determinations of cardiac output were made. The dye was injected via the catheter, and arterial samples were collected at 2-second intervals. Serum concentration was read at 620 m μ , with correction for hemolysis at 540 m μ on a Beckman DU spectrophotometer.⁷ In one patient (O.S.) the cardiac output was determined by the Fick method, the mixed venous sample being obtained from the pulmonary artery. Stroke volume was calculated from the cardiac output and simultaneously recorded heart rate. Total peripheral resistance (dynes-seconds cm.⁻⁵) was calculated from the mean blood pressure and cardiac output.

Each subject was studied before and after 2 mg. of atropine sulfate in 5 ml. of sterile water was delivered via the catheter over a 1-minute interval. Data on the effect of atropine in recumbency (3 to 25 minutes after injection) were obtained during 22 studies on 20 subjects (Table I). For the purposes of this study the changes observed at this time interval were considered to be a *delayed response* to atropine.

In order to elucidate further the circulatory changes produced by atropine, additional studies were performed. Eighteen of the 20 subjects mentioned above and 2 additional subjects (E.J. and W.H.) were divided into two groups to determine whether the response produced by atropine was dependent on the duration of time after injection (Group A), and whether the response could be altered by maneuvers which might increase venous return (Group B).

In Group A (7 subjects) the circulatory effect of atropine was studied at different time intervals following injection. Serial determinations of cardiac output and related parameters were made on each subject before the injection of atropine, from 1 to 3 minutes after completion of the injection (*initial response*), and again from 4 to 14 minutes after the injection (*delayed response*).

In Group B (13 subjects) the hemodynamic effect of maneuvers which might increase venous return from the legs and the splanchnic area was studied, before and after atropinization. Each subject was studied in one of the following three ways:

1. *Postural Changes:* Each of 4 subjects was studied (a) recumbent, (b) with the head and trunk recumbent and the lower extremities passively raised on a ramp inclined 20 degrees, and (c) in a head-down body tilt of 10 degrees. The three positions were always assumed in the order listed. Three minutes were allowed in each position for the attainment of a steady state (as demonstrated by constancy of pulse rate, arterial pressure, and central venous pressure) before the cardiac output was determined. The same three postures were assumed beginning 5 to 10 minutes after the injection of atropine, and the determinations were repeated in the same sequence.

2. *Hyperventilation:* Each of 5 subjects was studied before and during a 3-minute period of vigorous voluntary hyperventilation at a respiratory rate of 40 per minute (metronome). Previous observations from this laboratory⁸ have demonstrated that the blood pressure, mean central venous pressure, pulse, and cardiac output are stable after the first minute of hyperventilation; accordingly, observations were made from the first to third minute of hyperventilation before the injection of atropine and then again 5 minutes after atropinization.

TABLE I. CIRCULATORY CHANGES FOLLOWING 2 MG. OF ATROPINE SULFATE IN RECUMBENT SUBJECTS

SUBJECT	AGE (YR.)	WEIGHT (KG.)	HEIGHT (CM.)	TIME AFTER ATROPINE (MIN.)	HEART RATE (BEATS/MIN.)*		ARTERIAL BLOOD PRESSURE (MM. HG.)						CENTRAL VENOUS PRESSURE (MM. HG.)		CARDIAC OUTPUT (L./MIN.)		STROKE VOLUME (ML./BEAT)		PERIPHERAL RESISTANCE (DYN-SEC. CM. ⁻⁵)		MEAN CIR- CULATION TIME (SEC.)		CENTRAL BLOOD VOLUME (L.)
					C	A	SYSTOLIC			DIASTOLIC			MEAN		C	A	C	A	C	A	C	A	
							C	A	C	A	C	A	C	A									
G.T.	23	84	185	3	54	120	154	171	62	90	86	115	7.18	13.45	133	960	690	21.8	12.4	2.62	2.78		
P.W.	19	62	178	25	64	90	127	117	59	59	73	75	6.93	7.33	108	845	815	20.9	15.6	2.41	1.91		
C.F.	23	90	189	3	78	114							7.43	7.38	95			17.4	15.2	2.16	1.87		
R.F.	21	74	187	4	60	108	114	110	63	66	76	78	4.75	6.74	79	1,280	930	24.8	16.8	1.96	1.89		
P.F.	20	83	180	12	60	114	109	109	59	72	77	84	5.71	5.96	95	1,200	1,130	22.9	17.0	1.89	1.69		
L.W.	22	66	175	5	84	126	128	122	69	67	84	86	7.09	8.63	84	950	797	13.9	11.9	1.64	1.70		
W.D.	21	90	183	5	72	114	138	141	71	86	98	106	6.94	7.78	96	1,300	1,090	14.9	11.6	1.72	1.50		
L.B.	19	86	180	4	60	120	107	129	59	67	79	95	5.38	7.24	90	1,175	1,050	25.3	14.5	2.27	1.75		
T.P.	18	66	180	4	72	129	120	120	58	54	72	76	6.46	7.08	90	892	860	18.1	12.6	1.95	1.49		
B.S.	21	71	182	3	72	126	114	123	56	70	74	85	5.85	8.45	81	1,030	805	18.6	13.8	1.81	1.94		
C.R.	20	64	171	10	65	111							5.61	8.37	86			20.0	13.5	1.87	1.87		
I.M.	21	75	185	10	68	110	132	140	72	80	92	100	5.50	7.94	81	1,340	1,000	20.8	14.5	1.91	1.92		
E.C. ₁	28	69	176	5	63	105	121	131	64	70	84	89	4.75	6.41	76	1,410	1,110	18.5	13.1	1.47	1.41		
E.C. ₂		66	176	15	65	107	121	117	62	74	84	90	5.64	6.85	87	1,230	1,050	17.7	13.0	1.66	1.48		
J.B. ₁	21	89	176	6	72	120	123	117	66	65	80	84	7.28	8.05	101	877	833	13.0	13.5	1.58	1.82		
J.B. ₂		86	176	10	69	114	112	108	64	68	80	81	6.10	8.37	89	1,050	775	16.7	11.3	1.70	1.58		
C.S.	18	102	192	4	58	120	144	130	58	57	80	85	6.69	9.49	115	955	706	20.0	15.9	2.24	2.51		
J.L.	24	63	182	4	102	165	117	109	56	42	74	67	9.56	9.23	94	618	582	13.1	10.1	2.08	1.56		
O.S.†	30	56	154	7	100	140							4.66	5.74	47								
J.H.	18	68	170	4	60	114	129	106	62	51	84	69											
K.W.	19	77	182	11	46	102							5.15	9.82	112			20.5	10.7	1.76	1.75		
H.H.‡	34	70	173	10	69	115	116	116	68	76	84	89	4.50	5.63	65	1,490	1,260	16.0	14.1	1.20	1.32		
Mean	22	75	179	7	69	117	124	123	63	67	81	86	6.15	7.90	91	1,084	911	18.7	13.6	1.90	1.79		
±S.D.	4	12	8	5	13	15	12	16	5	12	7	12	1.22	1.73	18	228	185	3.6	1.9	0.34	0.35		
P					<0.001	>0.5	<0.1	<0.05	<0.001	<0.001	<0.001	<0.001	<0.01	<0.001	<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.1		

*C: Control. A: Following atropine. The same designation is used for all subsequent parameters.

†Female patient. Cardiac output by Fick method.

‡Male patient.

3. *Albumin Infusion:* Each of 4 subjects was studied before and after the rapid intravenous infusion (given over a period of 4 to 9 minutes) of 25 or 50 Gm. of salt-poor human serum albumin diluted with normal saline to 200 and 400 milliliters, respectively, and observations were made from 4 to 15 minutes thereafter. In 2 subjects (J.B. and C.S.) atropine was given prior to albumin. In order to define further the possible role of an expanded plasma volume, the infusion of albumin was given first in one subject (W.H.), and in another (E.J.) it was given in two increments of 25 Gm. each, before and after the injection of atropine, with observations after each infusion.

All data were subjected to statistical analysis using the Student *t* distribution and the evaluation of the null hypothesis. Numerical data in the text are expressed as the mean plus-or-minus one standard deviation.

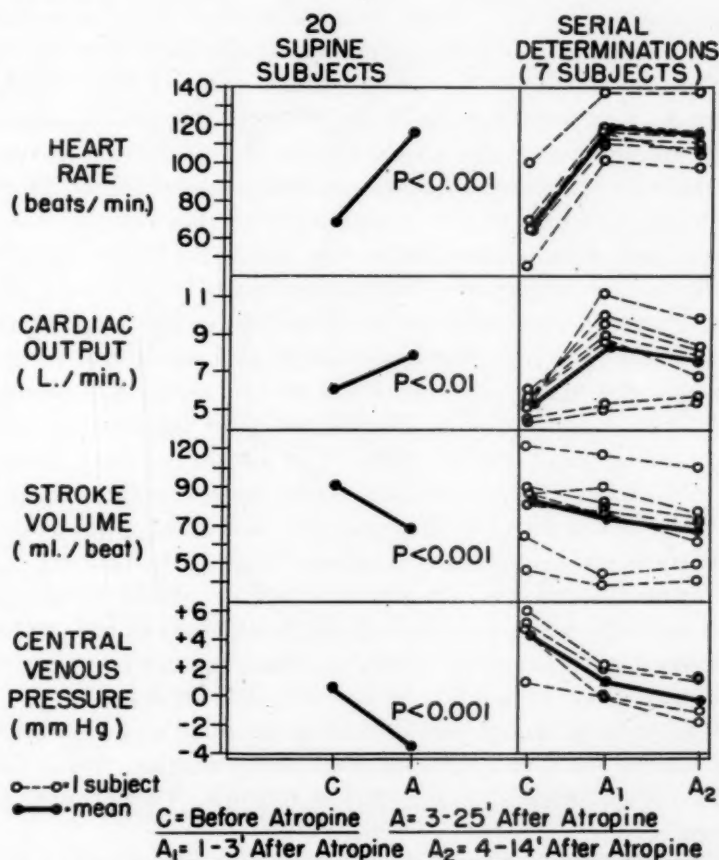


Fig. 1.—Various hemodynamic effects of 2 mg. of atropine sulfate in recumbent subjects.

RESULTS: THE EFFECTS OF ATROPINE IN RECUMBENCY

1. *Delayed Response to Atropine* (Table I and Fig. 1).—The following statistically significant changes were observed 3 to 25 minutes after the central venous injection of 2 mg. of atropine: (1) The heart rate increased in all subjects (mean rise, 49 ± 10 beats per minute), the tachycardia beginning before the end of the injection period and remaining at a relatively constant level for approximately 30 minutes. (2) The mean central venous pressure, which was stable prior to the administration of atropine, fell in the 16 studies in which it was measured (mean

fall, 4 ± 1 mm. Hg), decreasing rapidly before the end of the 1-minute injection period (by which time the tachycardia was maximum) and continuing to fall more slowly until the end of the experiment. (3) The cardiac output increased in 17 of 21 studies, the rise being quite variable, with a mean of 1.8 ± 1.6 liters per minute. Four subjects (P.W., C.F., P.F., and J.L.) showed no significant change from resting values. (4) The stroke volume fell in all 21 instances (mean fall, 23 ± 11 ml. per beat).

Other statistically significant alterations were a rise in mean arterial pressure (average increase, 5 ± 9 mm. Hg), a fall in total peripheral resistance (mean fall, 174 ± 116 dynes-seconds cm^{-5}), and a decrease in mean circulation time (average decrease, 5 ± 3 seconds). Variable changes, statistically not significant, were observed in "central blood volume" and systolic and diastolic arterial pressure.

II. *Group A. Comparison of the Initial With the Delayed Response to Atropine (Fig. 1).*—The changes in Group A were similar to those noted above, except for quantitative differences in the cardiac output and stroke volume. During the first 3 minutes following the injection of atropine the cardiac output in each of the 5 normal subjects rose considerably (mean rise, 4.0 ± 1.2 L. per minute). Repeat determinations on each of the same 5 normal subjects from 4 to 14 minutes after the injection of atropine revealed a subsequent fall in cardiac output to a lower level (mean fall from the determinations made at 3 minutes: 1.3 ± 0.4 L. per minute). During the first 3 minutes, there was no significant change in stroke volume ($P > 0.5$), but from 4 to 14 minutes after injection a significant fall was observed (pre-atropine control value, 91 ± 12 ml. per beat, falling to 77 ± 7 ml. per beat, $P < 0.02$). In an identical study, however, the 2 hospital patients developed a tachycardia with but little increase in cardiac output during the first 3 minutes after atropinization (in O.S. it rose from 4.7 L. to 5.3 L. per minute, and in H.H., from 4.5 to 5.6 L. per minute), and the stroke volume fell (in O.S. it fell from 47 to 38 ml. per beat, and in H.H., from 65 to 44 ml. per beat). Both the cardiac output and the stroke volume in these 2 patients remained at similar levels when observations were made 10 minutes after atropine.

In the 4 subjects in whom central venous pressure was measured, there was a marked fall during the first 3 minutes after atropinization (mean fall, 3.1 ± 1.5 mm. Hg) and a slight additional fall (1.3 ± 0.5 mm. Hg) occurring during the next 7 minutes.

III. *Group B. The Effect of Maneuvers Intended to Increase Venous Return (Fig. 2).*—

1. *Postural Changes (head-down tilt and passive leg-raising):* In 3 of the 4 subjects these maneuvers produced no significant changes from the values observed during recumbency. However, in 1 subject (L.W.) both of these postures produced an increase in cardiac output after the injection of atropine, restoring to normal the lowered stroke volume (Fig. 2).

2. *Hyperventilation:* Hyperventilation produced a much greater rise in cardiac output (mean rise, 6.2 ± 1.9 L. per minute) than did atropine (mean rise, 1.8 ± 2.6 L. per minute), although both produced a similar tachycardia. The stroke volume was maintained with hyperventilation but fell with atropine (control, 102 ± 17 ml. per beat; hyperventilation, 111 ± 14 ; atropine, 74 ± 24 ml. per

beat). Hyperventilation *after* atropinization was less effective in raising cardiac output (mean rise, 3.0 ± 1.2 L. per minute) than hyperventilation without atropine, in spite of an even greater tachycardia (before atropine, 112 ± 12 beats per minute; after atropine, 138 ± 13 beats per minute). Hyperventilation failed to alter the atropine-induced fall in stroke volume (during hyperventilation after atropine: 68 ± 7 ml. per beat).

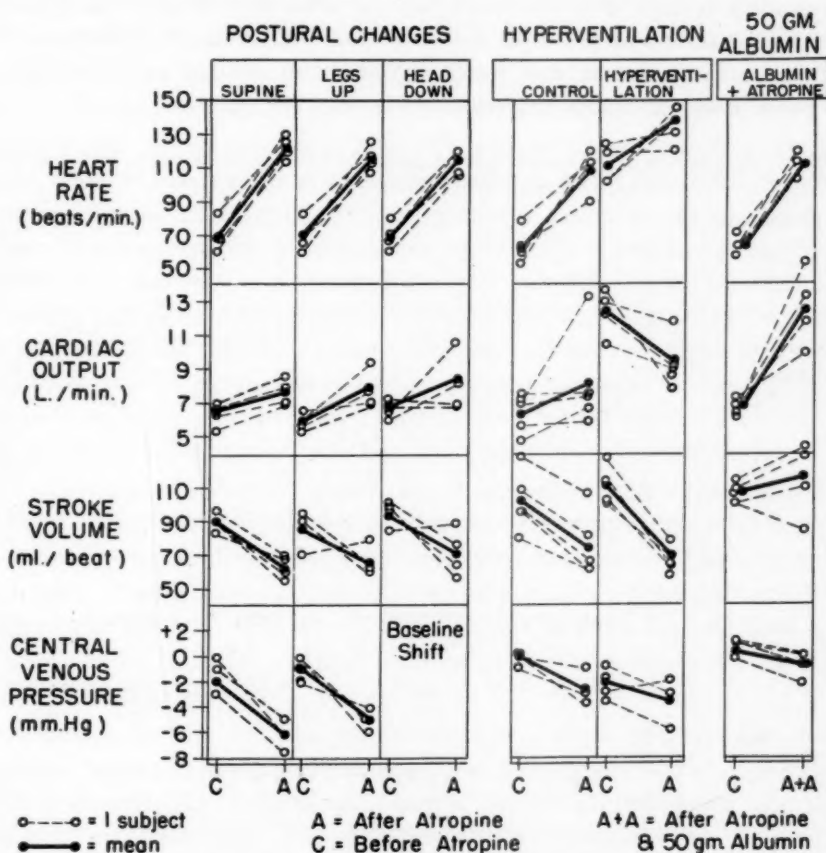


Fig. 2.—The effect of maneuvers intended to increase venous return in normal subjects before and after atropinization.

3. *Albumin Infusion* (Table II and Fig. 2): In 2 subjects (J. B. and C. S.) atropinization resulted in the expected increase in cardiac output and fall in stroke volume and central venous pressure (see Table II). Fifty grams of albumin were infused rapidly while the effects of atropine were still evident, with resultant increases in cardiac output (1.9 and 5.8 L. per minute, respectively), venous pressure (2 and 3 mm. Hg), and stroke volume (20 and 55 ml. per beat) over the levels observed after the injection of atropine. The effect of reversal of this procedure was studied in a third subject (W.H.) who was given 50 Gm. of albumin *before* the injection of atropine. Albumin alone produced an increase in cardiac output of 2.9 L. per minute, with little change in heart rate, a rise in venous pressure (4 mm. Hg), and an increase in stroke volume (22 ml. per beat). Atropine then

produced an even greater increase in cardiac output (4.1 L. per minute) and a decrease in venous pressure and stroke volume from the level observed after the infusion of albumin. To ascertain the importance of the quantity of albumin infused, a fourth subject (E.J.) was studied after an infusion of 25 Gm. of albumin. No changes were observed except an increase in venous pressure. Atropine was then given, with the result (see Table II) similar to that seen in subjects given only atropine; a second infusion of 25 Gm. of albumin then resulted in changes similar to those noted above with 50 Gm. of albumin after atropine. In all 4 subjects the cardiac output was much higher after albumin *and* atropine than after albumin alone or atropine alone.

TABLE II. THE EFFECT OF ATROPINE AND ALBUMIN ON CARDIAC OUTPUT, STROKE VOLUME, AND CENTRAL VENOUS PRESSURE IN 4 SUBJECTS

	SUBJECT	CONTROL	ATROPINE	PLUS ALBUMIN*
C.O. (L./min.)	J.B. ₁	7.28	8.05	9.99
S.V. (ml./beat)		101	67	87
C.V.P. (mm. Hg)		+1	-2	0
C.O.	C.S.	6.67	9.49	15.30
S.V.		115	79	134
C.V.P.		0	-5	-2

	SUBJECT	CONTROL	ALBUMIN	PLUS ATROPINE	AND ALBUMIN*
C.O. (L./min.)	W.H.	6.48	9.37	13.46	—
S.V. (ml./beat)		101	123	112	—
C.V.P. (mm. Hg)		+1	+5	0	—
C.O.	E.J.	6.91	6.35	9.92	11.34
S.V.		110	102	89	130
C.V.P.		+1	+3	-2	0

*Infusions of 50 Gm. in all subjects except E. J., who received two infusions of 25 Gm. each.

DISCUSSION

Small parenteral doses of atropine (0.3 to 0.6 mg.) have been shown to cause a bradycardia in most subjects,^{9,10} whereas larger doses (usually 1 mg. or more) produce a tachycardia. The effect of a large dose of atropine on the cardiac output in recumbent man was first reported in 1928, by Smith, Burwell, and DeVito,¹ using an indirect Fick method. Later, Suarez and co-workers² used the acetylene method, and McMichael and Sharpey-Schafer³ and Kelly and Bayliss⁴ used the direct Fick method in similar studies. All of the aforementioned workers observed that atropine (1 mg. or more parenterally) produced a marked tachycardia which was associated in most individuals with an increase in cardiac output. Stroke volume fell in most instances. More recently, Gorlin¹¹ studied six patients, three

of whom had heart disease, in whom atropine caused tachycardia but no rise in cardiac output. Direct Fick and dye dilution methods were used. Weissler, Leonard, and Warren⁵ found that cardiac output (dye dilution technique) did not rise in tilted subjects after atropine, whereas a considerable increase was seen in similar observations on recumbent subjects. They were able to produce an increase in cardiac output in atropinized tilted subjects by inflation of a lower-body antigravity suit. Gordon and his associates¹² found that 2 or 3 mg. of atropine given intramuscularly resulted in postural hypotension which could be largely overcome, in similar fashion, by inflation of an antigravity suit.¹³ In all of these studies,³⁻⁵ when central venous pressure was measured, it decreased after atropine.

The present study confirms previous reports that atropine (2 mg. intravenously) results in an increase in cardiac output, a fall in stroke volume, and a decrease in central venous pressure in recumbent subjects. It should be emphasized that the rise in cardiac output is not invariable. Cardiac output did not rise after atropine in the above-mentioned study by Gorlin,¹¹ in an occasional subject in this study (see Table I), nor in a few subjects in the reports by McMichael and Sharpey-Schafer³ and Kelly and Bayliss.⁴ However, these studies are not comparable in regard to the age of the subjects (differences in vagal tone could be considerable) or dosage of atropine (ranged from 1 to 3 mg.). Twenty of the 22 subjects in the present study were healthy male university students.

It is of interest that when cardiac output was measured in five normal subjects within 3 minutes after the injection of atropine, the output was higher than when it was measured again 4 to 14 minutes after injection, although the tachycardia did not lessen. These observations apparently account for the differences between our studies and those of Weissler, Leonard, and Warren,⁵ who found a marked increase in cardiac output with no change in stroke volume within 3 minutes after the injection of atropine.

The mechanism by which atropine produces these effects remains obscure. Tachycardia and an increase in cardiac output accompany anxiety, exercise, fever, and thyrotoxicosis. In these situations the metabolic needs are also increased. In contrast, atropine does not significantly increase oxygen consumption.^{1,14} Therefore, the increased cardiac output after atropine could hardly be due to a response to increased metabolic demand.

One might postulate that the increase in cardiac output following atropine occurs through as yet unknown mechanisms to maintain a normal blood pressure in the face of a falling peripheral resistance. Atropine might cause the peripheral vascular bed to dilate by a direct effect on blood vessels or by a ganglionic blocking action, causing local increases in peripheral flow. The fact that arterial pressure is maintained after atropinization (in recumbent subjects) is consistent with this concept. An alternative hypothesis is that atropine actually limits the amount of blood returning to the heart, perhaps by a peripheral pooling action, so that there is less blood for the heart to pump with each beat. Hence, the cardiac output could increase after atropine only because of the increase in heart rate. This increase would not be of the same magnitude as that observed in the other types of tachycardia mentioned previously, because of the limited venous return.

A third and less likely explanation for the limited increase in cardiac output and fall in stroke volume is the possibility of an alteration of ventricular function by atropine. We have no data pertinent to this point, but if such a myocardial change does occur, it is apparently easily overcome by the infusion of albumin (see Fig. 2).

The explanation of the fall in venous pressure which occurs in the presence of a rise in cardiac output is not evident. It is well known that a fall in central venous pressure does not necessarily imply that venous return is decreased, and that the observed central venous pressure may not be a true measure of the effective distending pressure. Preliminary attempts by the authors to measure venous distending pressure following the administration of atropine have been unsuccessful, since the measurement of intrapleural pressure was indirect (esophageal balloon) and esophageal tone was apparently altered by the drug.

If the relative decrease in cardiac output and the fall in stroke volume observed later than 3 minutes after atropine were due to a decrease in venous return, such as would occur from vascular pooling in the legs and splanchnic bed, one might expect the cardiac output and stroke volume to increase during maneuvers intended to increase venous return from these areas. This was not the case in our study on hyperventilation after atropine, and, with a single exception, cardiac output and stroke volume were not increased in atropinized subjects by passive leg-raising or head-down tilting. Since the latter maneuvers produced little or no hemodynamic change before atropine, however, their lack of success in producing an increase in venous return was less surprising. The results of rapid intravenous infusion of albumin, on the other hand, would tend to indicate that cardiac output and stroke volume may be strikingly increased in atropinized subjects by increasing venous return in this manner. Since the number of subjects studied was small and the possibility of additional side effects from the infusion of albumin cannot be ruled out, further studies on this point would be necessary before definite conclusions could be drawn.

SUMMARY AND CONCLUSIONS

1. Central venous injection of 2 mg. of atropine sulfate in 22 recumbent subjects produced a tachycardia associated with an increase in cardiac output, a fall in stroke volume, a decrease in mean central venous pressure, and a slight rise in mean arterial pressure, when observations were made from 3 to 25 minutes after injection.

2. In five normal subjects the increase in cardiac output was greater during the first 3 minutes after atropine than from 4 to 14 minutes after the injection, although the pulse rate remained essentially unchanged. Thus, an absolute fall in stroke volume occurred later than 3 minutes after the injection of atropine.

3. Certain maneuvers intended to increase venous return (hyperventilation, passive leg-raising, and head-down tilting) failed to increase cardiac output or stroke volume after the injection of atropine.

4. In contrast, rapid infusion of 50 Gm. of serum albumin produced a marked increase in minute volume and stroke volume in a small group of atropinized subjects.

5. Alternative hypotheses are suggested to explain ways by which atropine might act to produce the circulatory changes mentioned above.

The authors wish to express their gratitude for the helpful advice of Dr. Eugene A. Stead, Jr., and Dr. Arnold M. Weissler, and for the technical assistance of Mrs. Jean Smith, Mrs. Jane Whalen, Mrs. Elizabeth Gilbert, Miss Virginia Johnston, and Mrs. Elizabeth Steiner.

REFERENCES

1. Smith, W. C., Burwell, C. S., and DeVito, M. J.: The Effect of Atropine Upon the Output of the Hearts of Normal Men, *J. Clin. Invest.* **6**:237, 1928.
2. Suarez, J. R. E., Taquini, A. C., and Fasciolo, J. C.: La accion de la atropina sobre el volumen minuto cardiaco, *Rev. argent. cardiol.* **10**:291, 1943.
3. McMichael, J., and Sharpey-Schafer, E. P.: Cardiac Output in Man by a Direct Fick Method; Effects of Posture, Venous Pressure Change, Atropine, and Adrenaline, *Brit. Heart J.* **6**:33, 1944.
4. Kelly, H. G., and Bayliss, R. I. S.: Influence of Heart Rate on Cardiac Output; Studies With Digoxin and Atropine, *Lancet* **2**:1071, 1949.
5. Weissler, A. M., Leonard, J. J., and Warren, J. V.: Effects of Posture and Atropine on the Cardiac Output, *J. Clin. Invest.* **36**:1656, 1957.
6. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Studies on the Circulation. IV. Further Analysis of the Injection Method, and of Changes in Hemodynamics Under Physiological and Pathological Conditions, *Am. J. Physiol.* **99**:534, 1932.
7. Gibson, J. G., II, and Evelyn, K. A.: Clinical Studies of the Blood Volume. IV. Adaptation of the Method to the Photoelectric Microcolorimeter, *J. Clin. Invest.* **17**:153, 1938.
8. Gleason, W. L., Berry, J. N., Mauney, F. M., and McIntosh, H. D.: The Hemodynamic Effects of Hyperventilation, *Clin. Res.* **6**:127, 1958.
9. McGuigan, H.: Effect of Small Doses of Atropine on Heart Rate, *J.A.M.A.* **76**:1338, 1921.
10. Petzatakis, M.: La phase stimulatrice de l'atropine, *Presse méd.* **24**:548, 1916.
11. Gorlin, R.: Studies on the Regulation of the Coronary Circulation in Man. I. Atropine-Induced Changes in Rate, *Am. J. Med.* **25**:37, 1958.
12. Kalser, M. H., Frye, C. W., and Gordon, A. S.: Postural Hypotension Induced by Atropine Sulfate, *Circulation* **10**:413, 1954.
13. Miller, R. D., Kalser, M. H., Frye, C. W., and Gordon, A. S.: Measurement of Atropine-Induced Vascular Pooling, *Circulation* **10**:423, 1954.
14. Sturgis, C. C., Wearn, J. T., and Tompkins, E. H.: Effects of the Injection of Atropine on the Pulse Rate, Blood Pressure and Basal Metabolism in Cases of "Effort Syndrome," *Am. J. M. Sc.* **158**:496, 1919.

Effects of Thiouracil and Sitosterol on Diet-Induced Hypercholesterolemia and Lipomatous Arterial Lesions in the Rat

Maurice M. Best, M.D., and Charles H. Duncan, M.D., Louisville, Ky.

The traditional concept that the rat is essentially immune to the experimental production of hypercholesterolemia and atheromatous arterial lesions must be revised in the light of recent evidence. Thus, Page and Brown¹ reported that dietary supplements of cholesterol and sodium cholate fed for an 8-month period to rats rendered hypothyroid by iodine¹³¹ resulted in significant hypercholesterolemia (mean, 1,486 mg./100 ml.) and extensive lipid infiltration of arterial walls. However, no foam cells or intimal proliferation was noted. More recently, other investigators employing a variety of semisynthetic diets containing cholesterol, and also including thiouracil in most instances, have reported the production not only of lipid deposits in arterial walls but also proliferative reactions more nearly resembling human atherosclerosis.²⁻⁴

The present study was undertaken to delineate the degree of hypercholesterolemia resulting from a representative "atherogenic" diet high in saturated fat and cholesterol. The extent to which the thiouracil employed by most investigators contributes to the hypercholesterolemia was also examined by feeding the same basic diet with and without thiouracil.

In view of the demonstrated inhibitory effect of sitosterol on the hypercholesterolemia resulting from cholesterol feeding in the hypothyroid rat⁵ the effect on the incidence of arterial lesions of the addition of this plant sterol to the diet was also studied.

METHODS

Four diets were employed.

I. Laboratory chow.*

II. Diet A. This was a semisynthetic diet consisting of the following ingredients: butter, 40.0 per cent; sucrose, 23.7 per cent; casein, vitamin free†, 20.0 per cent; cholesterol‡, 5.0 per cent; cellulose‡, 4.0 per cent; salt mixture W‡, 4.0 per cent; vitamin mixture‡, 2.0 per cent; choline chloride‡, 1.0 per cent; sodium cholate, 0.3 per cent.

From the Department of Medicine, University of Louisville School of Medicine, Louisville, Ky. Supported by research grants from the U. S. Public Health Service (H-1946), the Heart Association of Louisville and Jefferson County, and Eli Lilly and Company.

Received for publication April 24, 1959.

*Rat-Mouse ration. Harlan Small Animal Industry, Cumberland, Ind.

†Nutritional Biochemicals, Cleveland, Ohio.

III. Diet A plus thiouracil. Two grams of thiouracil was incorporated in each 1,000 grams of Diet A.

IV. Diet A plus thiouracil and sitosterol. Two grams of thiouracil and 50 grams of sitosterol, predominantly beta, was incorporated in each 1,000 grams of Diet A.

In the preparation of the diets the dry ingredients were thoroughly mixed by tumbling, and then blended into the butter. Diets were stored in closed containers under refrigeration for periods of no longer than 2 weeks.

Twenty-four male rats (Holtzman) ranging in weight from 140 to 150 grams were separated into groups of 6, the animals in each group being housed together in a large mesh-bottomed cage in a controlled-temperature room. Each group received one of the four diets ad libitum. Fresh food and tap water were provided daily. At the end of the 15-week feeding period the animals were anesthetized with intraperitoneal amobarbital sodium, and blood was obtained by cardiotomy. The heart and kidneys were removed and fixed in cobalt-formalin solution. The thyroid glands were carefully dissected free of fat and connective tissue, being protected against drying by moist filter paper, and weighed to the nearest 0.1 milligram in covered bottles. The liver was removed, blotted, and weighed, and with a sharp scalpel a 1 to 2-gram portion was cut for determination of cholesterol content.

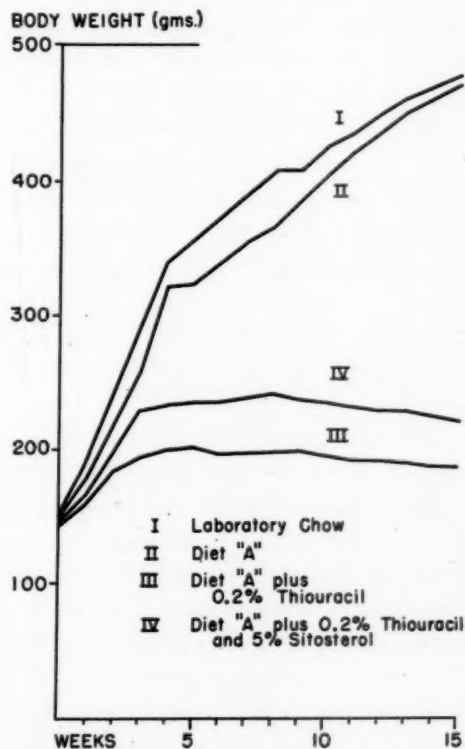


Fig. 1.—Effect of the experimental diets on mean gain in weight. The inhibitory effect of thiouracil on growth of Groups III and IV is apparent.

Serum cholesterol was determined by the method of Abell and associates.⁶ The liver segment was homogenized in 1:1 acetone-ethanol by means of a high-speed blender, and free and total cholesterol were determined by the method of Sperry and Webb.⁷

Hearts and kidneys were identified by code numbers and forwarded to Dr. W. Stanley Hartroft for microscopic study. Four to six sections of each heart and two of each kidney were cut with the freezing microtome, stained with oil red O, and counterstained with hematoxylin and a light green. The presence or absence of abnormal deposits of lipid in arterial walls and of myocardial or renal infarcts was determined without access to the identifying key.

TABLE I. EFFECTS OF THE VARIOUS EXPERIMENTAL DIETS FED FOR PERIODS OF 15 WEEKS*

GROUP	DIET	SERUM CHOLE- STEROL (MG./100 ML.)	LIVER CHOLESTEROL (MG./100 GM.)		LIVER WEIGHT (GM.)	THYROID WEIGHT (MG./100 GM.)	STAINABLE LIPID IN ARTERIAL WALLS		
			FREE	TOTAL			HEART	KIDNEY	INFARCTION
			(MG./100 GM.)	(MG./100 GM.)			(NUMBER OF RATS)		
I	Laboratory chow	54 ± 5	215 ± 10	235 ± 14	13.9 ± 1.1	5.4 ± 0.5	0	0	0
II	Diet A	279 ± 127	479 ± 65	12,774 ± 2,728	26.8 ± 1.9	5.5 ± 0.7	1	0	0
III	Diet A plus thiouracil	1,589 ± 691	462 ± 127	5,526 ± 1,632	11.1 ± 1.7	48.0 ± 15.0	3	4	3
IV	Diet A plus thiouracil and sitosterol	517 ± 329	323 ± 38	3,382 ± 1,083	10.2 ± 1.0	30.6 ± 9.0	2	0	0

*Values given are the mean ± the standard deviation estimated using (n - 1) for groups of 6 rats.

An additional group of 4 animals received Diet A plus thiouracil for a period of 24 weeks. At the end of the 24-week period one animal was killed, and the diet of the remaining 3 changed to laboratory chow. At the end of 5, 14, and 21 days after the return to a diet of laboratory chow one animal was killed. Determination of serum and liver cholesterol of these animals was performed by the above-mentioned methods.

RESULTS AND DISCUSSION

As to gain in weight, activity, and general appearance the rats which were fed the high-fat and high-cholesterol semisynthetic diet (Group II) did not differ appreciably from those of the control group maintained on laboratory chow (Fig. 1). The tremendous capacity of the rat to store excess cholesterol in the liver is demonstrated by these animals. The livers were grossly fatty and were approximately twice normal weight. The mean total cholesterol content was over one hundred times that of the animals fed laboratory chow, the greater part of the increment being in the ester fraction (Table I).

The increase in serum cholesterol, while statistically significant ($P < .01$), was of much lesser magnitude. None of the animals in this group exhibited infarction of heart or kidney, and the only arterial abnormality noted on microscopic study was the presence in one animal of small droplets of fat in the sub-intima and media of a branch of a coronary artery.

The animals in Group III (Diet A plus 0.2 per cent of thiouracil) exhibited lacklustre coats and diminished activity and failed to gain weight normally (Fig. 1). The goitergenic effect of thiouracil is clearly demonstrated in the increased thyroid weights of this group (Table I). Comparison of these animals with those in Group II reveals that the addition of thiouracil resulted in significantly higher mean serum cholesterol and significantly lower mean liver total cholesterol ($P < .01$).

That an elevation of serum cholesterol occurs in hypothyroidism has been documented by a number of observers, and the hypercholesterolemic effect of thiouracil has generally been attributed solely to its antithyroid properties. A recent report⁸ from this laboratory indicated that thiouracil also exerts a hypercholesterolemic effect which is independent of its suppression of thyroid activity. Thus, in the athyreotic rat, thiouracil produced an increase in serum cholesterol and a decrease in liver cholesterol, presumably due to a shift in the plasma-liver cholesterol pool from liver to plasma.⁸

The enhanced hypercholesterolemia resulting from the addition of thiouracil to Diet A was accompanied by an increase in the incidence of arterial lesions. Half of the animals in this group demonstrated microscopic renal infarcts, and in 4 of the 6 there were lipid deposits in the arterial walls of either the heart or kidney, or both.

Thomas and Hartroft,⁹ employing a diet very similar to that fed to Group III, described the occurrence of myocardial as well as renal infarcts, 6 of 10 animals displaying either or both. Mean serum total cholesterol in the two animals surviving to the end of the experimental period was more than twice that observed in our series. The lower serum total cholesterol levels and the failure to obtain myocardial infarction in the present study may be the result of any

one of several differences in the experimental protocol, notably a different strain of rats and a higher choline and lower sodium cholate content of the diet.

Group IV received the same diet as the preceding group of animals except for the addition of sitosterol. An inhibitory effect of sitosterol on the accumulation of cholesterol in serum and liver is manifest, the mean levels being significantly lower than in Group III ($P < .01$ for serum cholesterol and $P < .05$ for liver cholesterol). It should be noted that sitosterol is precipitated by digitonin and gives the Liebermann-Burchard color reaction; thus, "cholesterol" as determined by the methods employed would include to a great extent any sitosterol present in serum or liver.

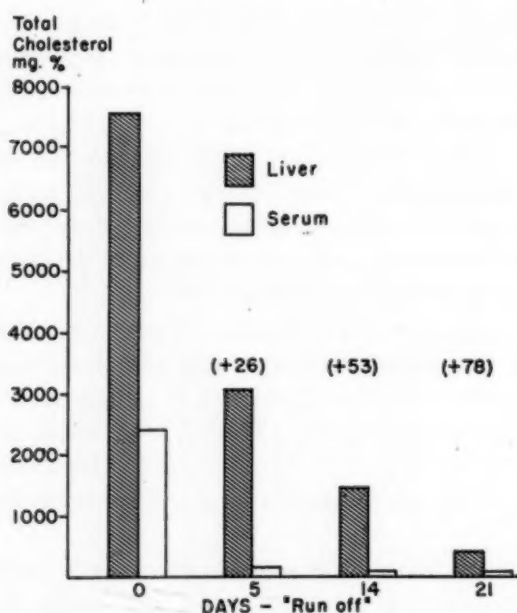


Fig. 2.—Rapid return toward normal of serum and liver cholesterol following substitution of laboratory chow for Diet A plus thiouracil. Represented are values for individual rats fed the high saturated fat and cholesterol diet plus 0.2 per cent of thiouracil for 24 weeks, and killed at 0, 5, 14, and 21 days after return to the laboratory chow diet. Figures in parentheses are gains in weight in grams during the "runoff" period.

In previous studies it was observed that 5 per cent of sitosterol essentially completely inhibited the increase in serum and liver cholesterol of the hypothyroid rat which otherwise occurred on a diet of 1 per cent cholesterol.⁵ This effect of sitosterol is assumed to be due to its interference with the absorption of cholesterol from the intestinal tract, as demonstrated by Hernandez and associates¹⁰ using cholesterol-4-C¹⁴. That the inhibition of cholesterol accumulation in serum and liver in the present study was incomplete can be attributed at least in part to the lower ratio of sitosterol to cholesterol in the diet employed (approximately 5:6).¹¹

The possibility that sitosterol may also interfere with the absorption of thiouracil is suggested by the significantly ($P < 0.05$) smaller mean thyroid weight of Group IV. The mean gain in weight of this group was also somewhat greater

than that of Group III, although the difference is not statistically significant ($P > 0.10$). However, any possible inhibition of the effect of thiouracil by sitosterol cannot account for the reduced liver cholesterol observed, since increased rather than decreased liver cholesterol would be expected to result from interference with thiouracil effect.

Although any conclusions as to the incidence of arterial lesions must be tentative because of the small size of the groups, it would appear that sitosterol effected a definite reduction not only in serum cholesterol but also in the incidence of arterial lesions. In the rabbit, sitosterol has been shown to exert a similar inhibitory effect on the development of hypercholesterolemia and atheromata consequent to cholesterol feeding.¹²

A remarkable ability of the rat to rapidly eliminate an excess of cholesterol in serum and liver was demonstrated by the group of 4 animals maintained on Diet A plus thiouracil for 24 weeks and then returned to laboratory chow (Fig. 2). This is particularly dramatic as regards serum cholesterol; the rat killed only 5 days after return to a diet of laboratory chow had a serum cholesterol of only 135 mg./100 ml. This capacity of the rat to rapidly eliminate cholesterol and to store any excess in the liver accounts no doubt for the relative difficulty in inducing hypercholesterolemia and atheromatous lesions.

SUMMARY

A semisynthetic diet high in saturated fat and cholesterol was fed to albino rats for 15 weeks. A moderate increase in serum cholesterol and a marked increase in liver cholesterol resulted. Microscopic examination of heart and kidney revealed minimal lipid deposition in arterial walls in only 1 of 6 animals.

The incorporation of 0.2 per cent of thiouracil in the diet resulted in significantly higher levels of serum cholesterol and a reduced concentration of cholesterol in the liver. Of the 6 animals in this group, 3 displayed microscopic renal infarcts, and in 4 of them lipomatous arterial lesions were found in either heart or kidney, or in both.

The further addition of 5 per cent of sitosterol to the diet partially inhibited the accumulation of cholesterol in serum and liver, and decreased the incidence of arterial lesions.

The authors are indebted to Dr. W. Stanley Hartroft, Chairman, Department of Pathology, Washington University School of Medicine, St. Louis, Mo., for the preparation and interpretation of the microscopic sections.

REFERENCES

1. Page, I. H., and Brown, H. B.: Induced Hypercholesterolemia and Atherogenesis, *Circulation* **6**:681, 1952.
2. Wissler, R. W., Eilert, M. L., Schroeder, M. A., and Cohen, L.: Production of Lipomatous and Atheromatous Arterial Lesions in the Albino Rat, *A. M. A. Arch. Path.* **57**:333, 1954.
3. Fillios, L. C., Andrus, S. B., Mann, G. V., and Stare, F. J.: Experimental Production of Gross Atherosclerosis in the Rat, *J. Exper. Med.* **104**:539, 1956.
4. Hartroft, W. S., and Thomas, W. A.: Pathological Lesions Related to Disturbances of Fat and Cholesterol Metabolism in Man, *J.A.M.A.* **164**:1899, 1957.

5. Best, M. M., and Duncan, C. H.: Effects of Sitosterol on the Cholesterol Concentration in Serum and Liver in Hypothyroidism, *Circulation* **14**:344, 1956.
6. Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E.: A Simplified Method for the Estimation of Total Cholesterol in Serum and Demonstration of Its Specificity, *J. Biol. Chem.* **195**:357, 1952.
7. Sperry, W. M., and Webb, M.: A Revision of the Schoenheimer-Sperry Method for Cholesterol Determination, *J. Biol. Chem.* **187**:97, 1950.
8. Duncan, C. H., and Best, M. M.: Effect of Thiouracil on Serum and Liver Cholesterol of the Athyreotic Rat, *Am. J. Physiol.* **194**:351, 1958.
9. Thomas, W. A., and Hartroft, W. S.: Myocardial Infarction in Rats Fed Diets Containing High Fat, Cholesterol, Thiouracil, and Sodium Cholate, *Circulation* **19**:65, 1959.
10. Hernandez, H. H., Peterson, D. W., Chaikoff, I. L., and Dauben, W. G.: Absorption of Cholesterol-4-C¹⁴ in Rats Fed Mixed Soybean Sterols and Beta-Sitosterol, *Proc. Soc. Exper. Biol. & Med.* **83**:498, 1953.
11. Best, M. M., and Duncan, C. H.: Effects of the Esterification of Supplemental Cholesterol and Sitosterol in the Diet, *J. Nutrition* **65**:169, 1958.
12. Pollak, O. J.: Successful Prevention of Experimental Hypercholesterolemia and Cholesterol Atherosclerosis in the Rabbit, *Circulation* **7**:696, 1953.

A Relation Between the Auscultatory Gap and the Pulse Upstroke

Simon Rodbard, M.D., Ph.D., and Jan Ciesielski, M.D., Buffalo, N. Y.

The auscultatory gap has been demonstrated to be associated with diminished flow of blood to the extremity.¹ Thus, gaps could be induced in some individuals with arteriosclerotic heart disease by using a tourniquet to reduce the flow of blood to the forearm. Furthermore, the gap could always be eliminated by increasing the flow of blood by inducing a local reactive hyperemia.

Examination of phonarteriographic records² obtained in patients with auscultatory gaps suggested that in addition to a reduced flow of blood to the extremity, the occurrence of a gap was also associated with an abnormal contour of the arterial pulse upstroke.

METHODS

The calibrated upstroke of the arterial pulse wave in 45 patients with systolic hypertension or aortic stenosis was graphically constructed according to a technique described previously.² The patients were at rest (R) in a supine position. The cardiac mechanism was regular sinus rhythm. The blood pressure cuff was inflated to a level higher than systolic and permitted to fall at a rate of 2 to 3 mm. Hg per second. The arterial sounds at the antecubital fossa were recorded by dynamic microphone at uniform amplifier gain and at a paper speed of 50 mm. per second. Lead II of the electrocardiogram was taken simultaneously as a reference tracing. The momentary level of the falling column of mercury in the sphygmomanometer was noted by introducing standardization voltages into the electrocardiographic tracing at intervals of 5 mm. Hg.

The time in hundredths of a second from the onset of the ventricular complex (Q) of the electrocardiogram to the beginning of the arterial sound (K) was determined from the record. By plotting this Q-K time for each beat against the momentary level of the cuff pressure, synthetic calibrated contours of the upstroke of the pulse wave were constructed. The contour could also be visualized by drawing a line which connected the onset of all the arterial sounds, as noted previously.² The term "synthetic" is used to indicate that the contour obtained by our method is the synthesis of a sequence of individual points obtained in successive pulses as the cuff pressure falls.

RESULTS

Systolic Hypertension.—Auscultatory gaps were noted in 2 of 18 patients with high blood pressures (Table I, Patients 1 and 2). In both of these patients

From the University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y. (The Institute is supported in part by the New York State Department of Health.)

This study was aided by Grant H-2271 from the National Heart Institute of the United States Public Health Service.

Received for publication May 8, 1959.

the gap was present at blood pressure levels of approximately 170 mm. Hg (Fig. 1,A). Reactive hyperemia induced by exercise (E), by having the patient open and close the fist 20 times in about 20 seconds, eliminated the gap in all instances (Fig. 1,B). In Patient 3, with arteriosclerotic systolic hypertension and a relatively normal diastolic pressure, the gap was between 130 and 110 mm. Hg.

Elicited gaps: In 7 of the patients with systolic hypertension in whom no gap was evident on first examination (Table I, Patients 4 to 10) a gap could be elicited by reducing the flow of blood into the extremity. This reduction in flow was accomplished by placement of a tourniquet (T) on the forearm. This procedure reduced the amplitude and duration of all the arterial sounds (compare

TABLE I. SYSTOLIC HYPERTENSION

PATIENT	SEX	AGE (YR.)	DIAGNOSIS†	CONDI- TION‡	BLOOD PRESSURE (MM. Hg)		
					SYSTOLIC	GAP	DIASTOLIC
1. A.B.	F	56	HCVD, Asthma	R	225	172-156	124
				T	225	188-152	132
				E	225	—	120
2. J.B.	M.	70	HCVD, ASHD	R	210	180-170	100
				T	210	185-140	100
				E	210	—	100
3. L.C.*	F	65	HCVD	R	160	130-110	100
4. E.C.	F	66	HCVD	R	190	—	105
				T	215	205-180	120
				E	195	—	110
5. F.S.	F	57	HCVD	R	230	—	115
				T	230	210-200	115
				E	235	—	120
6. H.M.	F	62	ASHD, Diabetes	R	185	—	90
				T	190	—	90
				E	190	—	90
7. A.W.	F	52	ASHD, Diabetes	R	190	—	95
				T	195	185-170	95
				E	195	—	105
8. S.T.	M	53	HCVD, Diabetes	R	220	—	100
				T	225	210-190	105
				E	220	—	100
9. A.W.	M	67	ASHD, HCVD	R	190	—	120
				T	190	180-140	120
				E	190	—	120
10. E.F.	F	67	ASHD	R	280	—	80
				T	280	250-240	85

*The autopsy findings were hypertensive cardiovascular disease with marked passive congestion of lungs, liver, spleen, and intestines.

†HCVD: Hypertensive cardiovascular disease. ASHD: Arteriosclerotic heart disease.

‡R: Patient supine, at rest. T: Placement of tourniquet on upper forearm to reduce flow of blood to extremity. E: Exercise of arm.

A and B of Fig. 2). At the levels at which the gap was elicited, sound could not be heard, nor were vibrations observed on the phonarteriogram.

A shoulder on the upstroke of the pulse wave at the level of the auscultatory gap was demonstrated in every case. This is illustrated in Fig. 2, B as the wide difference of the Q-K time of 0.34 second at 215 mm. Hg to the Q-K time of 0.26 second at 200 mm. Hg. It may be visualized by joining the onset of each of the arterial sounds by a line which shows a sharp upstroke from 115 to 195 mm. Hg, and which then slopes off to 0.34 at 215 mm. Hg. The induced gaps usually extended 10 to 15 mm. Hg, and the shoulders represented halts in the upstroke of about 0.06 second in duration.

TABLE II. AORTIC STENOSIS

PATIENT	SEX	AGE (YR.)	CLINICAL DIAGNOSIS†	CONDI- TION‡	BLOOD PRESSURE (MM. Hg)		
					SYSTOLIC	GAP	DIASTOLIC
11. A.R.*	M	77	AS + ASHD	R	175	110-95	50
				T	175	145-105	65
				E	185	125-105	60
12. P.G.	M	63	AS	R	135	110-105	80
				T	140	130-115	85
				E	140	—	85
13. B.C.	M	69	AS + AI	R	190	150-135	60
14. L.M.	M	72	AS + AI	R	140	120-90	75
15. J.D.	M	62	AS	R	80	—	68
				T	92	86-76	68
				E	92	—	68
16. B.R.	M	53	AS + AI	R	145	—	65
				T	140	120-105	50
				E	140	—	45
17. R.S.	F	42	AS + AI, RHD	R	145	—	65
				T	150	125-115	65
				E	155	—	65
18. G.G.	M	43	AS, MS, MI, RHD	R	140	—	65
				T	150	115-105	70
				E	145	—	75

*Autopsy demonstrated moderately severe calcific aortic stenosis.

†AS: Aortic stenosis. ASHD: Arteriosclerotic heart disease. AI: Aortic insufficiency. RHD: Rheumatic heart disease. MS: Mitral stenosis. MI: Mitral insufficiency.

‡R: Patient supine, at rest. T: Placement of tourniquet on upper forearm to reduce flow of blood to extremity. E: Exercise of arm.

Aortic Stenosis.—Diagnosis of aortic stenosis was based on the medical history of a systolic thrill and a coarse murmur at the cardiac base, and by radiologic demonstration of calcification in the region of the aortic root. A spontaneous gap, illustrated in Fig. 3, A, was observed in 4 of 27 patients with clinical diagnoses of aortic stenosis. In these cases the shoulder usually represented a halt

in the upstroke of the pulse wave of about 0.04 second in duration. Exercise of the arm used for the determinations of blood pressure increased the amplitude and duration of the sounds and eliminated the gap in one of the two patients in whom this was done (Fig. 3,B). In the other patient the gap was relatively unaffected. After the application of a tourniquet to the forearm, which procedure presumably reduces the flow of blood to the part, the extent of the gap was increased in both patients (Fig. 3,C).

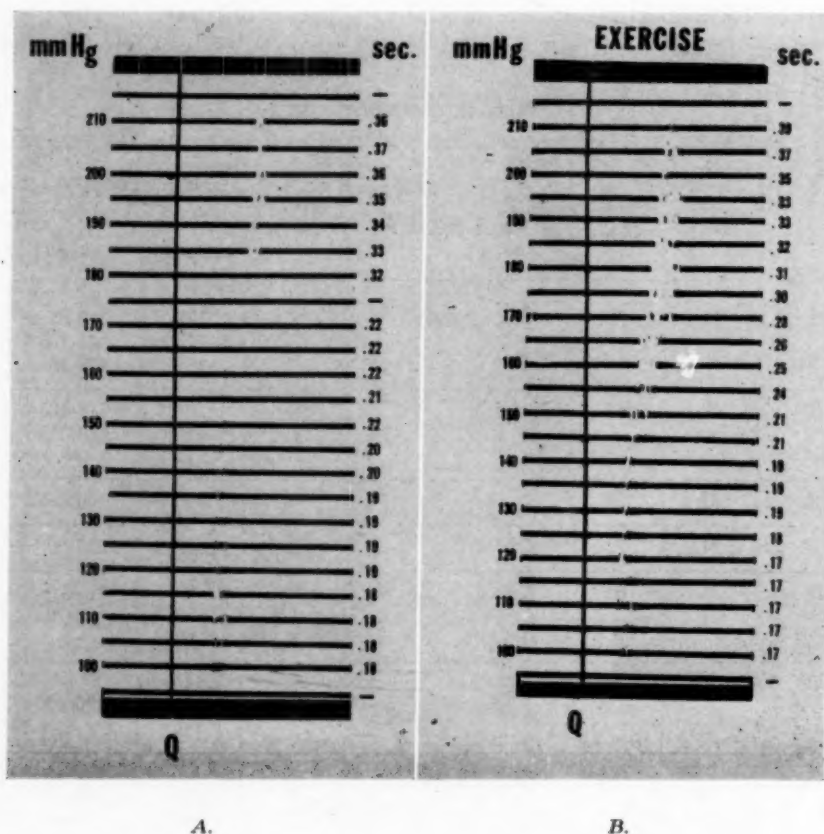


Fig. 1.—A, Auscultatory gap observed in Patient 2 (see Table I). Blood pressure was 210/100 mm. Hg. A long strip of record was obtained as the cuff pressure fell. Cuttings from this record were assembled so that each cycle was aligned with reference to the Q wave (vertical line). Cuff pressures are given at the left. Time of onset of the arterial sound (Q-K time) is given at the right. The definitely audible and recorded sounds from cuff pressure 210 to 185 mm. Hg disappeared for about 10 mm. Hg and then reappeared. Timing records are given above and below, the vertical lines being 0.04 second apart. A line connecting the onset of each of the sounds provides an estimate of the upstroke of the arterial pulse contour. B, Elimination of the gap during reactive hyperemia. A record on the same patient as in A. The increased intensity of the sounds is evident. Discussed in text.

Elicited gaps: The application of a tourniquet to the forearms of all the patients with diagnoses of aortic stenosis reduced the amplitudes and durations of the arterial sounds. In 4 of these an auscultatory gap was induced (compare A and B of Fig. 4). The shoulder on the upstroke at the pressure level of the gap is illustrated by graphing the onsets of the sounds in Fig. 4,C.

DISCUSSION

Because an auscultatory gap may introduce sources of error into the estimation of the blood pressure, this phenomenon has attracted attention for more than four decades.³ In 1928, Mudd and White⁴ reviewed the literature on the gap and noted its occurrence in hypertension, arteriosclerosis, and aortic stenosis. The mechanism of the gap was ascribed variously to the shape of the pressure curve, a reduced velocity of the pulse wave, the failure of resonance of the artery,³ angiospastic phenomena,⁴ and venous congestion in the arm.^{5,6}

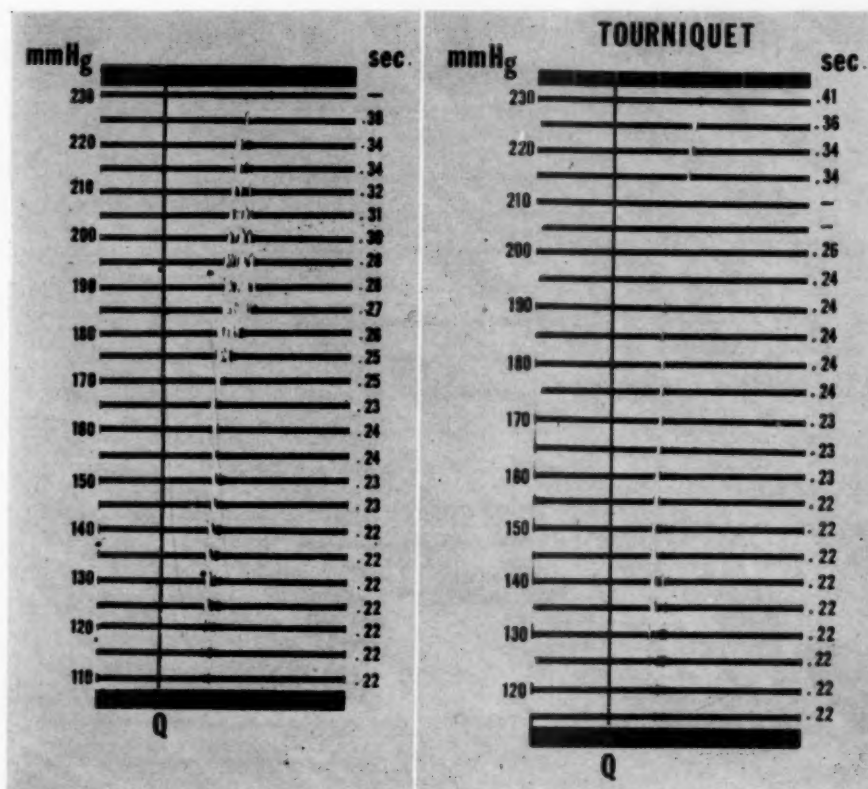


Fig. 2.—A, Arterial sounds obtained on a patient with the diagnosis of diastolic hypertension (Patient 5, Table I). B, Arterial sounds on the same patient after placement of a tourniquet on the forearm. Note the reduced durations of the sounds and the presence of a gap.

Analyses of recordings of the arterial vibrations heard during routine indirect measurement of blood pressure reveal that these sounds can usually be clearly divided into two components (Fig. 5): an onset snap of high amplitude and short duration, followed almost immediately by a low-pitched, relatively prolonged rumble. Both of these acoustic elements must be eliminated if a gap is to be noted in the usual train of arterial sounds.

Snap.—The onset snap of the arterial sounds is generated at the instant when the rising pulse wave exceeds the cuff pressure; the amplitude of this snap-

ping sound appears to depend on the slope of the rising pulse wave as the cuff pressure is exceeded. Thus, a steep pulse wave, as occurs in the lower levels of cuff pressure in cases with aortic insufficiency, produces loud snaps as it transits the levels of cuff pressure. This effect is seen in the break in the dark horizontal line which in Fig. 4,A represents the onset sound in the range of cuff pressure between 55 and 105 mm. Hg. However, the presence of a reduced slope at the point of crossing, as occurs at a shoulder on the upstroke of the pulse wave, results in a feeble or even subaudible snap (Fig. 3,A). This is particularly evident after placement of a tourniquet, as seen in Figs. 2,B, 3,C, and 4,B.

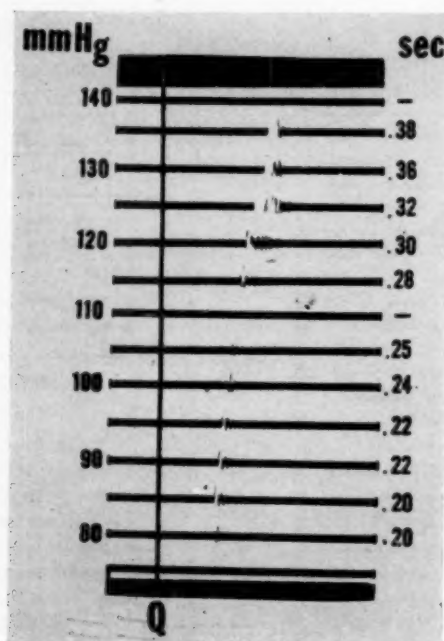


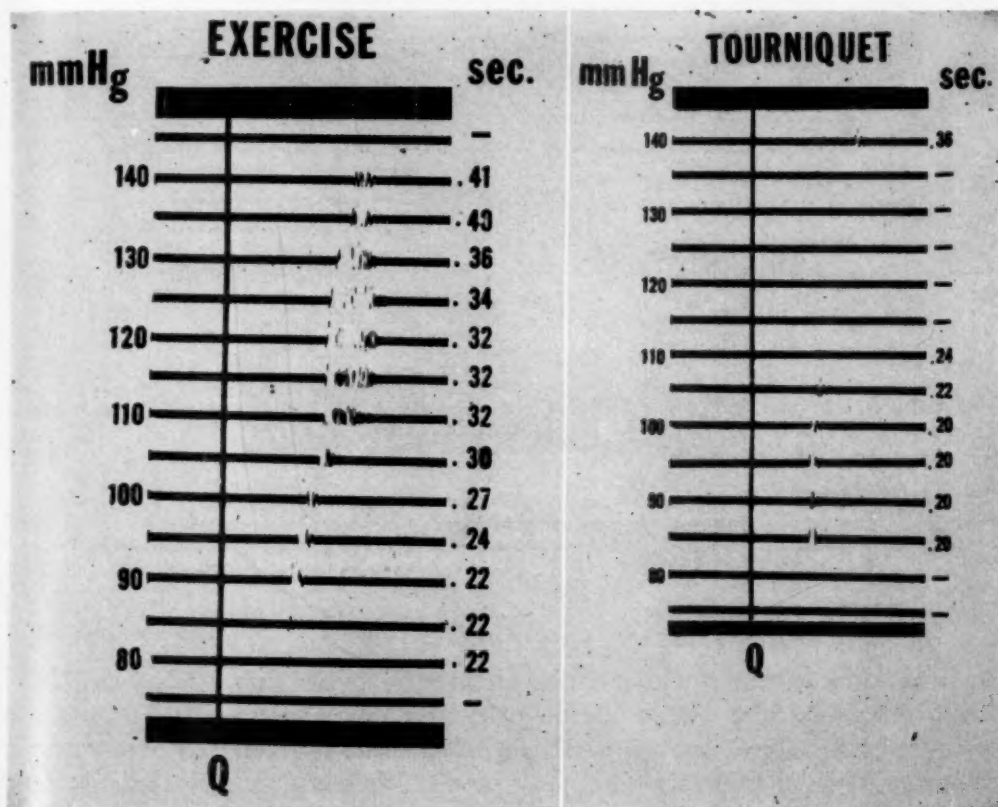
Fig. 3,A.—A spontaneous auscultatory gap in a patient with a diagnosis of aortic stenosis (Patient 12, Table II). Discussed in text.

Care must be taken to eliminate a tendency to artefact when auscultatory gaps are being recorded. Thus, acoustic recordings sometimes show a low-frequency vibration corresponding in time with the passage of the pulse wave across the level of cuff pressure. These are seen in the gaps in Figs. 1, 2,B, 3,C, and 4,B, and below the diastolic pressure in Figs. 3,C and 4,A. This slow wave does not represent an audible sound. However, an increase in amplifier gain can distort the wave and produce a "sound."

The mechanism of production of a shoulder on the upstroke has been discussed in detail in the physiological literature, but no consensus has been achieved. On the basis of previous studies of flow through collapsible and elastic tubes, we feel that the shoulder may be generated by hydrodynamic forces which produce recurrent closure of the aortic valves during the period of rapid ejection. This fluttering action of the valves is believed to disturb the usual smooth upstroke of the pulse wave.^{7,8} The resulting notching on the upstroke at the aortic

root is lost as a result of the damping characteristics of the elastic aorta, and the reduced slope of this segment of the upstroke may appear as a smooth shoulder when recorded at a peripheral artery. The mechanism of the shoulder in ventricular overload, as in hypertension, has not been elucidated.

Rumble.—The rumbling phase of the arterial sound which normally follows the onset snap is associated with the volume of blood flowing through the artery compressed by the cuff.⁹ This interpretation is supported by the finding that reduction of blood flow by application of a tourniquet reduces the duration of the rumble. Arterial vasospasm, as well as venous congestion of the arm resulting from a desultory raising of the cuff pressure prior to sphygmomanometric readings, can also diminish blood flow and thus enhance the likelihood of a gap.



B.

C.

Fig. 3, B and C.—Elimination of auscultatory gap seen in Fig. 3, A after the arm of Patient 12 had been exercised (B). Extension of the gap by application of a tourniquet on the forearm of the same patient (C). Discussed in text.

A reduced flow of blood into the extremity is likely to occur in association with the limited cardiac output of patients with cardiovascular disease. The flow of blood through the artery compressed by the cuff depends on the difference between the instantaneous arterial pressure and the level of the cuff pressure.

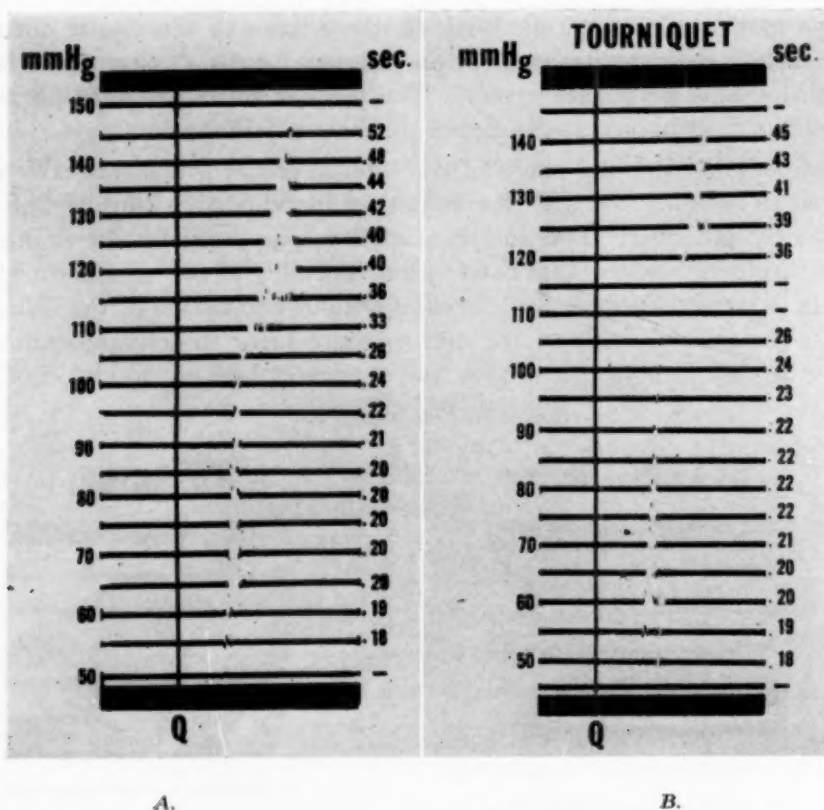


Fig. 4, A and B.—Arterial sounds of Patient 16 (A). Arterial sounds of the same patient after application of a tourniquet on the forearm (B).

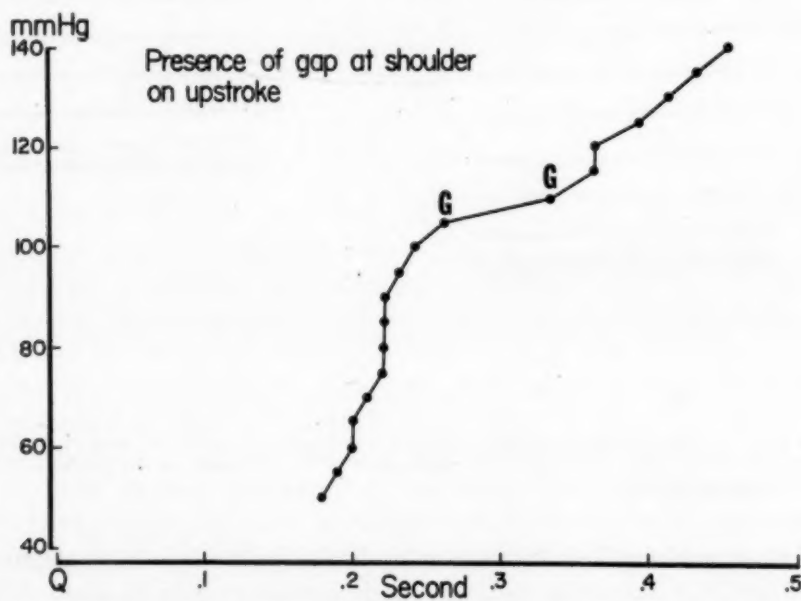


Fig. 4, C.—A drawing of the upstroke in Figs. 4, A and B, with expansion of the time base (horizontal axis) to illustrate the presence of the gap (G) at the level of the shoulder.

At the level of a shoulder on the upstroke of the pulse wave the gradient between arterial pressure and cuff pressure is small; flow is thereby minimal and the rumble is feeble or even nonaudible.

Further evidence for our thesis is the fact that the induction of reactive hyperemia by local exercise releases vasospasm and permits a more adequate flow of blood to the extremity, increasing the amplitude and duration of the rumbling noise and thereby tending to eliminate the gap (Figs. 1,*B* and 3,*B*).

These results demonstrate that auscultatory gaps represent a combination of a reduced flow of blood to the extremity and a shoulder on the upstroke of the pulse wave. The reduced flow of blood indicates a peripheral vasospastic tendency, while the shoulder may indicate a disturbance in cardiac action. The mechanisms involved in the selection of the specific gap range, and the amount of acoustic energy above and below the gap, continue under study.

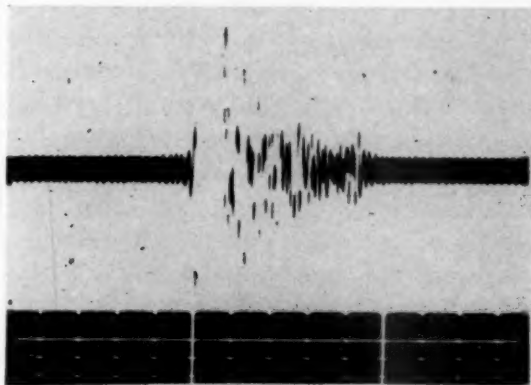


Fig. 5.—An arterial sound showing its two components: a brusque onset snap at the left is followed by a rumbling noise which is seen as the extended pattern of vibrations. Inspection by means of a hand lens of the arterial sounds in other figures shows separation of these two phases. Discussed in text.

SUMMARY

Auscultatory gaps noted in patients with systolic hypertension and in patients with aortic stenosis were studied by recording the arterial sounds during measurement of blood pressure, with electrocardiograms being recorded simultaneously as reference tracings. These records provided an indirect means for plotting a synthetic pulse wave contour. The results indicate that an auscultatory gap may occur when a shoulder on the upstroke of the pulse wave is associated with a reduced flow of blood to the extremity.

REFERENCES

1. Rodbard, S., and Margolis, J.: The Auscultatory Gap in Arteriosclerotic Heart Disease, *Circulation* 15:850, 1957.
2. Rodbard, S., Rubinstein, H. M., and Rosenblum, S.: Arrival Time and Calibrated Pulse Wave Contours Determined Indirectly by Arterial Sound Recordings, *AM. HEART J.* 53:205, 1957.
3. Cook, J. E., and Taussig, A. E.: Auscultatory Blood Pressure Determinations: A Source of Possible Error, *J.A.M.A.* 68:1088, 1917.

4. Mudd, S. G., and White, P. D.: The Auscultatory Gap in Sphygmomanometry, *Arch. Int. Med.* **41**:249, 1928.
5. Brim, C. J., and Wolffe, J. B.: The Silent or Auscultatory Gap, *Med. Rec.* **139**:113, 1934.
6. Berry, M. R.: The Mechanism and Prevention of Impairment of the Auscultatory Sounds During Determination of Blood Pressure of Standing Patients, *Proc. Staff. Meet. Mayo Clin.* **15**:699, 1940.
7. Rodbard, S., and Saiki, H.: Flow Through Collapsible Tubes, *AM. HEART J.* **46**:715, 1953.
8. Rodbard, S.: Transients as a Mechanism in the Production of Heart Sounds and Murmurs, *Circulation* **16**:282, 1957.
9. Rodbard, S.: The Significance of the Intermediate Korotkoff Sounds, *Circulation* **8**:600, 1953.

The Effect of Calcium Chloride on Experimental Extrasystoles With Constant Coupling

David Scherf, M.D., Diego De Armas, M.D., Bernard Garnier, M.D., William Sullivan, M.D., and Muhtar Yildiz, M.D., New York, N. Y.

While the effect of calcium on the resting and the action potential of heart muscle fibers is well known,^{15,18,26,29} our knowledge of the influence of calcium on extrasystoles and cardiac arrhythmias in general is scanty, and the available reports are contradictory. Extrasystoles are known to appear in man and in the experimental animal after the administration of calcium,^{3,13,14,19,20} but, on the other hand, under certain conditions they may disappear when calcium is administered. Thus, in the dog, atrial and ventricular extrasystoles caused by aconitine are promptly abolished when calcium is given intravenously, and simultaneously there is a marked improvement in the contractility of the heart muscle²²; clinically, calcium has been recommended for the therapy of paroxysmal tachycardia and fibrillation.³⁰ Calcium given intravenously may cause cardiac standstill.^{5,17} Because of these conflicting reports we decided to study the effect of calcium on veratrine-induced extrasystoles.

METHOD

The dogs were anesthetized with Nembutal and morphine, and the sternum was resected and the pericardium opened. The technique of injection of veratrine was the same as that described previously.^{23,25} Intravenous injection of veratrine does not cause persistent extrasystoles with constant coupling.²⁴ Topical application or subepicardial injection of veratrine leads within about a minute to a ventricular tachycardia, and extrasystoles with fixed coupling appear if at the same time the animal is made to breathe a mixture of 20 per cent carbon dioxide and 80 per cent oxygen. The calcium chloride was injected into the jugular vein in a 10 per cent solution. The electrocardiogram was registered in Lead II.

RESULTS

The experiments were performed on 18 dogs, and the results were uniform. In all the experiments the injection of 0.15 to 0.3 c.c. per kilogram of body weight of the solution of calcium chloride in the presence of coupled beats led to an increase in the number of extrasystoles lasting from 1½ to 6 minutes. When

From the Department of Medicine, New York Medical College, New York, N. Y.

This investigation was supported in part by a research grant from the National Heart Institute, United States Public Health Service.

Received for publication April 27, 1959.

after this interval the arrhythmia returned to its former pattern, a repetition of the injection had the same effect. However, a third injection led to the disappearance of the extrasystoles. Administration of an initially larger dose of calcium also abolished the extrasystoles. They often, but not always, reappeared after an interval of 15 to 20 minutes. They vanished completely when the veratrine-effect disappeared.

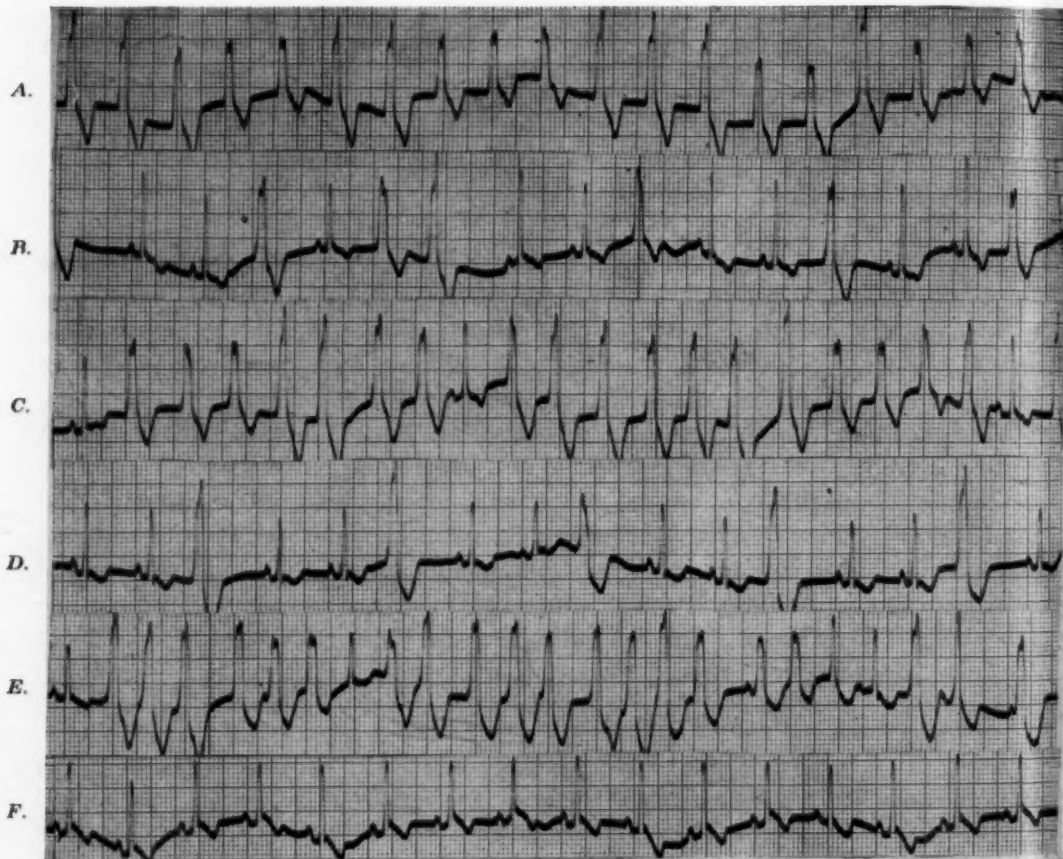


Fig. 1.—A, Regular ventricular tachycardia caused by focal application of veratrine on the right ventricle of a dog. B, Extrasystoles with fixed coupling appeared following inhalation of a mixture of oxygen with carbon dioxide. C, The intravenous injection of calcium chloride led to an increase of number and rate of the extrasystoles. D, Six minutes later a ventricular extrasystole appeared again regularly after every second sinus beat. E, A second injection of calcium chloride had the same effect as the first one. F, A third injection abolished the extrasystoles and caused changes of the ventricular complexes which are typical for high levels of calcium.

Fig. 1 shows tracings obtained from a typical experiment. The top tracing (Fig. 1,A) shows a regular ventricular tachycardia with a rate of 136, caused by the topical administration of veratrine; inhalation of the mixture of carbon dioxide and oxygen led to extrasystoles with fixed coupling (Fig. 1,B). One or two ventricular extrasystoles appeared with great regularity after every second sinus beat. Within a few seconds after the injection of 0.15 c.c. per kilogram of body weight of calcium chloride the number of extrasystoles increased markedly

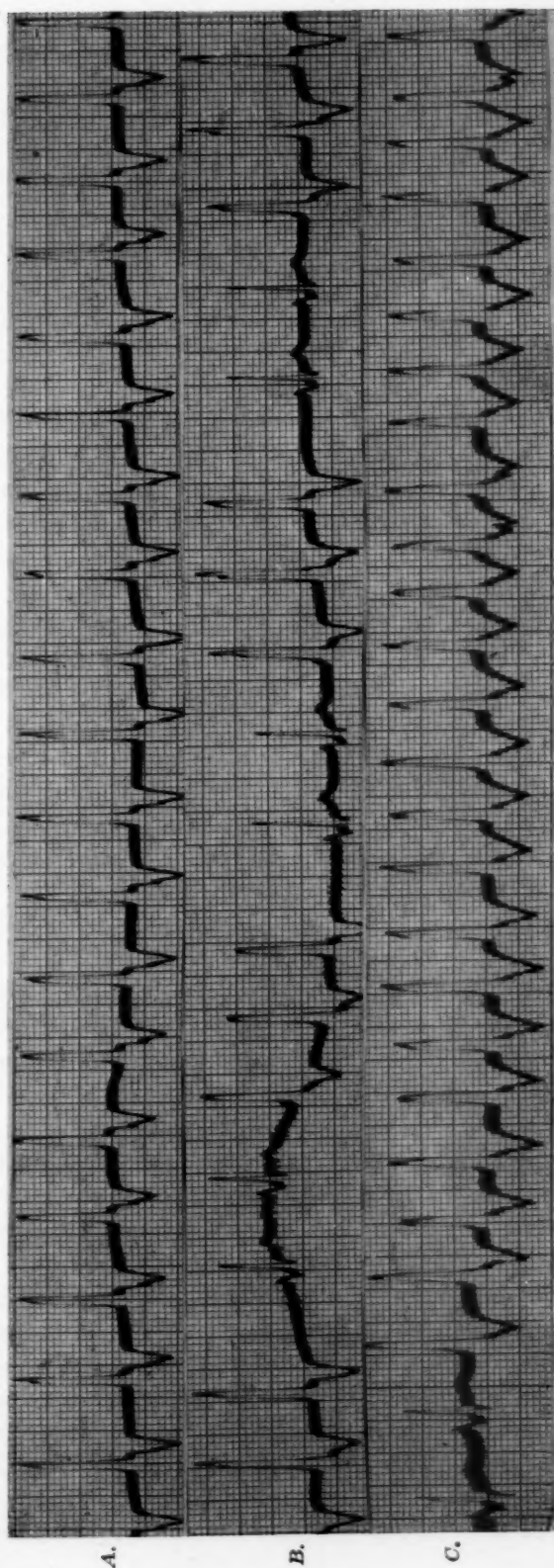


Fig. 2.—A, Regular ventricular tachycardia which appeared after focal application of veratrine. B, Series of three ventricular extrasystoles with fixed coupling are seen after every second sinus beat; this arrhythmia appeared after inhalation of the carbon-dioxide mixture for 6 minutes. C, The injection of 0.15 c.c. of the solution of calcium chloride per kilogram of body weight caused an attack of paroxysmal ventricular tachycardia.

(Fig. 1,C). The first beat was followed by 7 and the second one by 11 extrasystoles. The slight irregularity in form and the marked irregularity of rate were typical. After 6 minutes the arrhythmia returned to its former pattern; one extrasystole appeared after every second sinus beat (Fig. 1,D). At this point the injection was repeated in the same dosage, and a similar increase in the number and rate of the extrasystoles developed (Fig. 1,E). Eight minutes later, when the pattern had returned for 3 minutes to its former type (as in Fig. 1,D), a third injection of the same dose of calcium was given, and this time there was complete abolition of the extrasystoles, while the QRS complexes and the T waves showed the changes typical of high levels of calcium (Fig. 1,F).

Fig. 2 was taken during another experiment in which veratrine had caused a ventricular tachycardia with a rate of 120 beats per minute (Fig. 2,A). After the mixture of carbon dioxide and oxygen had been inhaled for 6 minutes, the arrhythmia shown in Fig. 2,B appeared. Three ventricular extrasystoles were seen regularly after every second sinus beat. The injection of calcium chloride in the amount of 0.15 c.c. per kilogram of body weight caused a ventricular tachycardia (Fig. 2,C) which disappeared after 2½ minutes. The complexes of the tachycardia were of the same form but appeared irregularly.

In the experiment from which Fig. 3 was taken the arrhythmia consisted of series of three or four ventricular extrasystoles appearing after several sinus beats. This was caused by the inhalation of the gas mixture for 4 minutes after administration of veratrine. At this point, 0.3 c.c. of calcium per kilogram of body weight was injected instead of the previous dose of 0.15 c.c. We saw a slight increase in the number of extrasystoles (Fig. 3,B), but the irregularities were greater and there were pauses which were equal to twice or three times the normal extrasystolic interval. Fig. 3,C was taken 2 minutes later and already showed a diminution in the number of extrasystoles.

DISCUSSION

In all experiments without exception the extrasystoles caused by veratrine and the carbon-dioxide mixture were increased by injection of smaller doses of calcium chloride, whereas larger doses suppressed them. The increase was temporary but could be reproduced by repeating the small dose. Larger doses led to complete suppression.

Much confusion exists in the literature since extrasystoles are often considered to be due to an "increased excitability" of the heart. Calcium, however, decreases excitability, and with higher levels of calcium a stronger electrical stimulus is necessary to elicit a response.^{11,15,20} The changes of excitability caused by an excess and a depletion of calcium are caused by changes in the critical level of the membrane potential at which depolarization occurs.²⁰ Therefore, the appearance of extrasystoles after the injection of calcium was considered unusual and could not be explained. In our opinion, extrasystoles are due to focal after-potentials and oscillations which reach threshold value and may arise even when the excitability to an outside stimulus is diminished. This same phenomenon is seen with digitalis, which depresses excitability while at the same time favoring formation of coupled beats. The depression of automaticity and the simultaneous

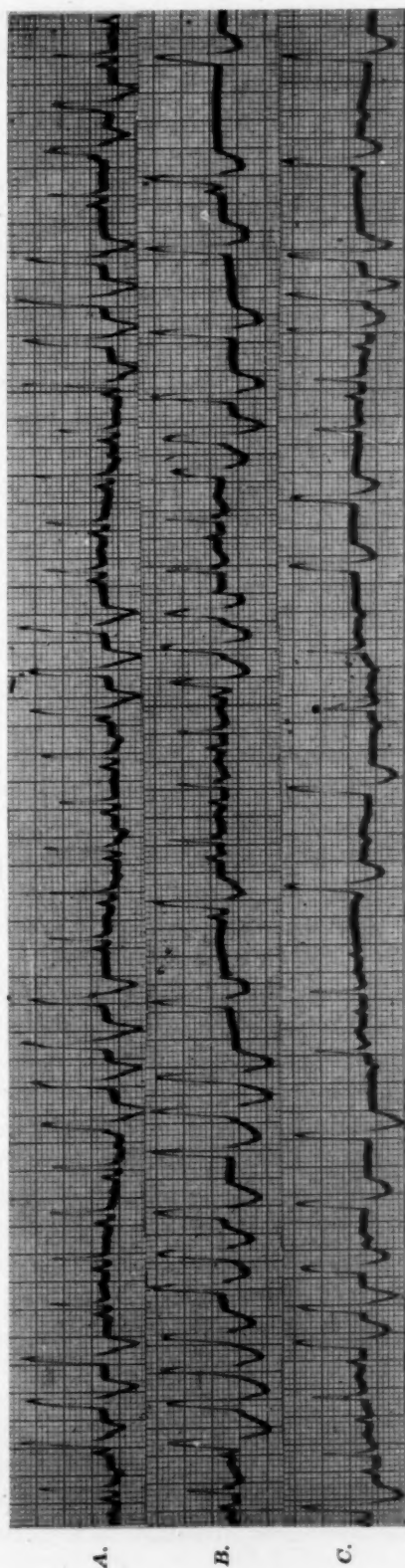


Fig. 3.—A shows series of three or four extrasystoles which had appeared after veratrine and inhalation of carbon dioxide for 4 minutes. The injection of 0.3 c.c. of calcium chloride per kilogram of body weight led to an increase in the number and rate of extrasystoles (B), and pauses between extrasystoles appear which are equal to two or three extrasystolic intervals. C was obtained 2 minutes later and shows a decrease in the number of extrasystoles.

formation of extrasystoles by calcium is best demonstrated in experiments on isolated strands of the specialized tissue of the dog: calcium given after veratrine inhibits automatic activity of this tissue; however, if an extracontraction is produced by application of a strong electrical stimulus, it is followed by a long chain of extrasystoles.⁸

The formation of oscillations and after-potentials is increased by *low* calcium, and one of the established methods for eliciting such after-potentials or extrasystoles consists in diminishing the calcium content of a nerve, an end-plate, skeletal muscle, or heart muscle by focal application of sodium oxalate or citrate.^{2,6,16,23} But under different experimental conditions, an increase in calcium increased the negative after-potential.^{6,9,18} Shanes²⁷ found that an increase in calcium depresses the naturally occurring negative after-potential but increases the veratrine-induced negative after-potential. However, by treating strips from the turtle heart with a solution containing an *excess* of calcium ions, Bozler obtained oscillatory after-potentials leading to discharge of chains of "extrasystoles."⁴ Therefore, our experiments on the mammalian heart *in situ* confirm these results. If calcium was said to be antagonistic to veratrine⁷ and to abolish the repetitive action of veratrine,²⁸ it appears clear from our data that the effect will depend on the dose.

A rapid injection of the calcium led in one of our experiments to paroxysmal atrial fibrillation, and in another experiment ventricular fibrillation appeared. This is in agreement with experimental findings¹⁰ that ventricular fibrillation can follow a rapid rise in extracellular calcium.

Rodeck,²¹ working on cold-blooded animals, found that small doses of calcium prolong the action potential, medium-sized doses cause at first a prolongation followed by a shortening, while large doses lead only to a shortening.

Harris and associates¹² injected an 8 times normal solution of calcium chloride into the coronary artery of an infarcted area in dogs. An increase of ectopic activity was found, sometimes followed by a reduction of extrasystoles.

A "dual action" of calcium on the heart is often stressed: following the administration of calcium some animals have inhibition of impulse formation and ventricular standstill, while others exhibit ventricular fibrillation.^{1,11,13} This phenomenon, however, can be observed with many other substances, such as digitalis, quinidine, procaine amide, and with another electrolyte, such as potassium. It can be explained by the above-mentioned property of calcium to decrease automaticity while enhancing the formation of extrasystolic impulses.

The appearance after the injection of calcium of the pauses between ectopic beats as seen in Fig. 3 (such pauses being equal to two or three interectopic periods) was observed in two other experiments. This "exit block" may explain the occurrence of cardiac standstill observed clinically after the intravenous administration of calcium.

CONCLUSIONS

Regular extrasystolic arrhythmias appeared in dogs with the heart *in situ* following focal application of veratrine and inhalation of a mixture of oxygen with 20 per cent of carbon dioxide. The intravenous injection of 0.15 to 0.3 c.c.

of calcium chloride per kilogram of body weight led to a temporary increase in the number of extrasystoles in all of the 18 experiments. Following the injection of larger doses the extrasystoles disappeared.

REFERENCES

1. Angelakos, E. T., Deutsch, S., and Williams, L.: Sensitivity of the Hypothermic Myocardium to Calcium, *Circulation Res.* **5**:196, 1957.
2. Arvanitaki, A.: Recherches sur la réponse oscillatoire locale de l'axone géant isolé de "sepia," *Arch. internat. de physiol.* **49**:209, 1939.
3. Berliner, K.: The Effect of Calcium Injections on the Human Heart, *Am. J. M. Sc.* **191**:117, 1936.
4. Bozler, E.: The Initiation of Impulses in Cardiac Muscle, *Am. J. Physiol.* **138**:273, 1943.
5. Bower, J. O., and Mengle, H. A. K.: The Additional Effect of Calcium and Digitalis, *J.A.M.A.* **106**:1151, 1936.
6. Brink, F.: The Role of Calcium Ions in Neural Processes, *Pharmacol. Rev.* **6**:243, 1954.
7. Fleckenstein, A.: *Der Kalium und Natrium-Austausch*, Berlin, 1955, Springer.
8. Goldenberg, M., and Rothberger, C. J.: Ueber die Wirkung von Veratrin auf den Purkinjefaden, *Arch. f. d. ges. Physiol.* **238**:137, 1937.
9. Graham, H. T.: Modification of Nerve After-Potential and Refractory Period by Changes of Ionic Environment: New Cases of Physiological Antagonism Between Univalent and Bivalent Cations, *Am. J. Physiol.* **104**:216, 1933.
10. Grumbach, L., Howard, J. W., and Merrill, V. I.: Factors Related to the Initiation of Ventricular Fibrillation in the Isolated Heart; Effect of Calcium and Potassium, *Circulation Res.* **2**:452, 1954.
11. Harris, A. S., and Madjerek, Z.: Effects of Added Calcium Upon the Intact Blood Circulated, Turtle Heart, *Am. J. Physiol.* **153**:402, 1948.
12. Harris, A. S., Toth, L. A., and Hoey, T. E.: Arrhythmic and Antiarrhythmic Effects of Sodium, Potassium, and Calcium Salts and Glucose Injected Into Coronary Arteries of Infarcted and Normal Hearts, *Circulation Res.* **6**:570, 1958.
13. Hoff, E. H., and Nahum, L. H.: An Analysis of the Cardiac Irregularities Produced by Calcium and Their Prevention by Sodium Amytal, *J. Pharmacol. & Exper. Therap.* **60**:425, 1937.
14. Hoff, H. E., Smith, P. K., and Winkler, A. W.: Electrocardiographic Changes and Concentration of Calcium in Serum Following Intravenous Injection of Calcium Chloride, *Am. J. Physiol.* **125**:162, 1939.
15. Hoffman, B. F., and Suckling, E. E.: Effect of Several Cations on Transmembrane Potentials of Cardiac Muscle, *Am. J. Physiol.* **186**:317, 1956.
16. Lehmann, J. E.: The Effect of Changes in the Potassium-Calcium Balance on the Action of Mammalian A Nerve Fibers, *Am. J. Physiol.* **118**:613, 1937.
17. Lloyd, W. D.: Danger of Intravenous Calcium Therapy, *Brit. M. J.* **1**:662, 1928.
18. Lorente de Nò, R.: A Study of Nerve Physiology, *Studies of the Rockefeller Institute for Med. Res.* **131**:122, 1947.
19. Malinow, M. R., Battle, F. F., and Malamud, B.: Nervous Mechanisms in Ventricular Arrhythmias Induced by Calcium Chloride in Rats, *Circulation Res.* **1**:554, 1953.
20. Malinow, M. R., Battle, F. F., and Malamud, B.: Standardized Method for Neurogenic and Cardiogenic Production of Ventricular Arrhythmias in the Rat, *Acta physiol. latinoam.* **3**:216, 1953.
21. Rodeck, H.: Ueber die Wirkung des Calciums auf den Aktionsstrom des Kaltbluterherzens, *Arch. f. d. ges. Physiol.* **249**:470, 1947.
22. Scherf, D.: Untersuchungen ueber die Entstehungsweise der Extrasystolen und der extrasystolischen Allorhythmien, *Ztschr. ges. exper. Med.* **65**:255, 1929.
23. Scherf, D., Blumenfeld, S., Golbey, M., Ladopoulos, C., and Roth, F.: Experimental Ectopic Cardiac Rhythms, *AM. HEART J.* **48**:573, 1954.
24. Scherf, D., Blumenfeld, S., Mueller, P., and Terranova, R.: Experimental Study on Ectopic Beats Following Intravenous Injection of Veratrine, *Proc. Soc. Exper. Biol. & Med.* **81**:701, 1952.
25. Scherf, D., Bussan, R., Gittinger, W. C., and Torin, S.: The Influence of Carbon Dioxide on Ectopic Tachycardias Caused by Veratrine, *AM. HEART J.* **51**:272, 1956.
26. Schütz, E.: Elektrophysiologie des Herzens bei einphasischer Ableitung, *Ergebn. Physiol.* **38**:493, 1936.
27. Shanes, A. M.: Electrochemical Aspects of Physiological and Pharmacological Action in Excitable Cells, *Pharmacol. Rev.* **10**:165, 1958.
28. Straub, R.: Die Wirkung von Veratridin und Ionen auf das Ruhepotential markhaltiger Nervenfasern des Frosches, *Helvet. physiol. et pharmacol. acta* **14**:1, 1956.
29. Weidmann, S.: Effect of Calcium Ions and Local Anesthetics on Electrical Properties of Purkinje Fibers, *J. Physiol.* **129**:568, 1955.
30. Wolffe, J. B., and Bellet, S.: Cessation of Attacks of Auricular Paroxysmal Tachycardia by the Use of Calcium, *Ann. Int. Med.* **4**:795, 1931.

Direct Epicardial and Thoracic Leads: Their Relationship in Man

Ennio Barbato, M.D., Antonio Carlos Debes, M.D., Toshiyasu Fujioka, M.D., Fulvio Pileggi, M.D., Euryclides de Jesus Zerbini, M.D., and Luiz V. Décourt, M.D., São Paulo, Brazil*

In previous papers¹⁻⁴ the QRS patterns in different points on the epicardial and juxtacardiac diaphragmatic surfaces of normal and pathologic human hearts were studied. In the present paper an attempt is made to compare in the same patients the records from those surfaces with the records obtained on the thoracic surface.

MATERIAL AND METHOD

The following 56 patients were studied: 28 who were normal, 8 with mitral stenosis, 7 with chronic cor pulmonale, 5 with Fallot's tetralogy, 1 with Fallot's trilogy, 1 with pure pulmonary stenosis, 1 with emphysema of the lung, 1 with double aortic lesion, 1 with essential hypertension, 1 with persistent ductus arteriosus without pulmonary hypertension, 1 with persistent ductus arteriosus with pulmonary hypertension, and 1 with atrioventricularis communis.

By means of the same instruments, technique, and method previously described²⁻⁴ the following leads were recorded: in 7 normal patients and in the patient with emphysema, only the diaphragmatic leads; in 4 normal patients, only epicardial leads of the atrium; and in the other patients particularly epicardial leads of the ventricles. The three standard leads, as well as Goldberger's unipolar leads, and from 60 to 84 thoracic leads throughout the chest, including Wilson's six precordial leads, were also recorded in all of the patients. The multiple thoracic leads were arranged in the figure as though the thorax had been opened at its midline posteriorly and completely extended anteriorly.

RESULTS

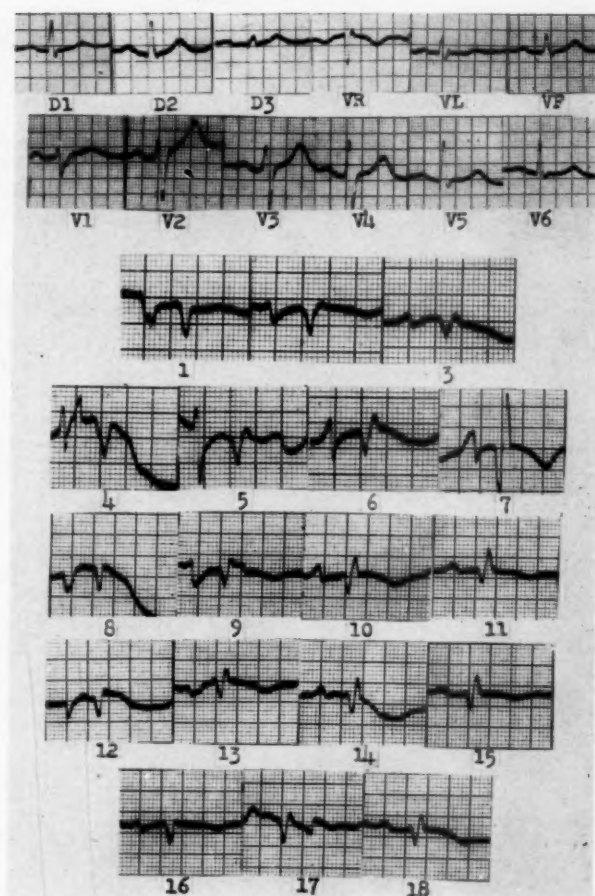
Since it is impossible to include illustrations of all of our cases, we selected only those of three normal patients, of one patient with right ventricular strain pattern, and of one with right bundle branch block (Figs. 1 to 5). Left ventricular hypertrophy patterns are very similar to those of normal cases.

All P and T waves and QRS complex morphologies found on the thoracic surface are also found on the epicardial surface. The distribution and sequence of each individual wave or complex obeys the same order on both surfaces. The areas with similar QRS complex morphologies also show similar T waves.

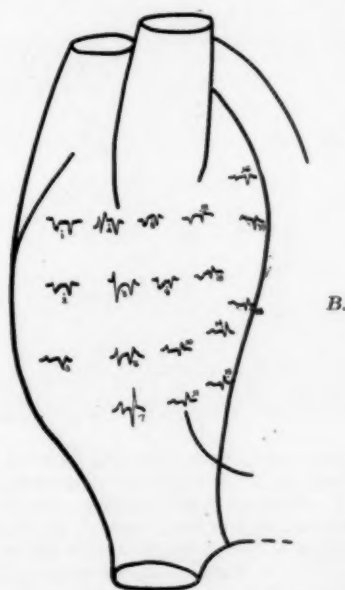
From the Department of Medicine, Section of Cardiology (Second Medical Division), Hospital das Clínicas, University of São Paulo, Faculty of Medicine, São Paulo, Brazil.

Received for publication April 1, 1959.

*From the Department of Surgery, Thoracic Section (First Surgery Division), Hospital das Clínicas, University of São Paulo, Faculty of Medicine, São Paulo, Brazil.



A:



B.

Fig. 1.—A and B. (For legend see page 240.)

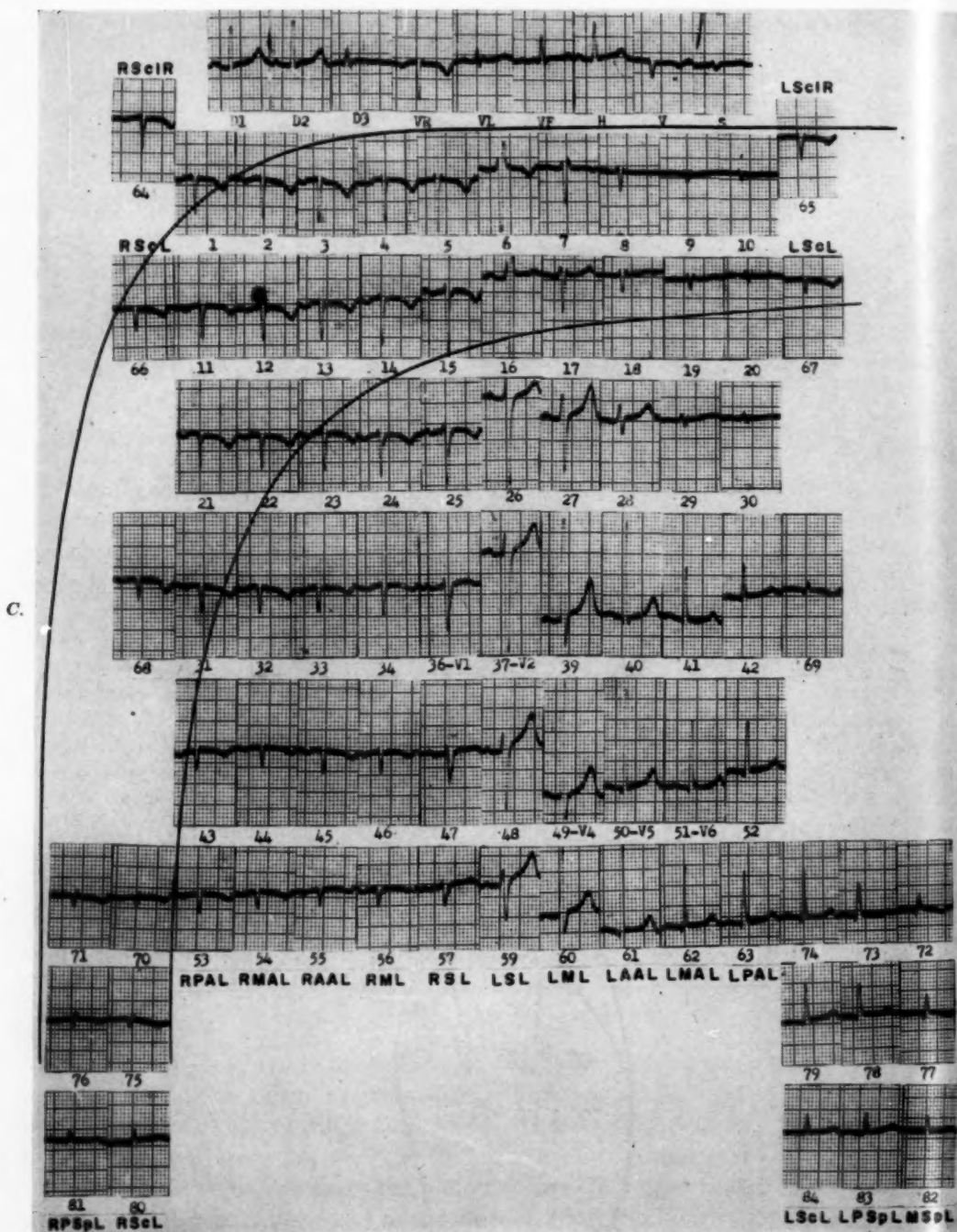
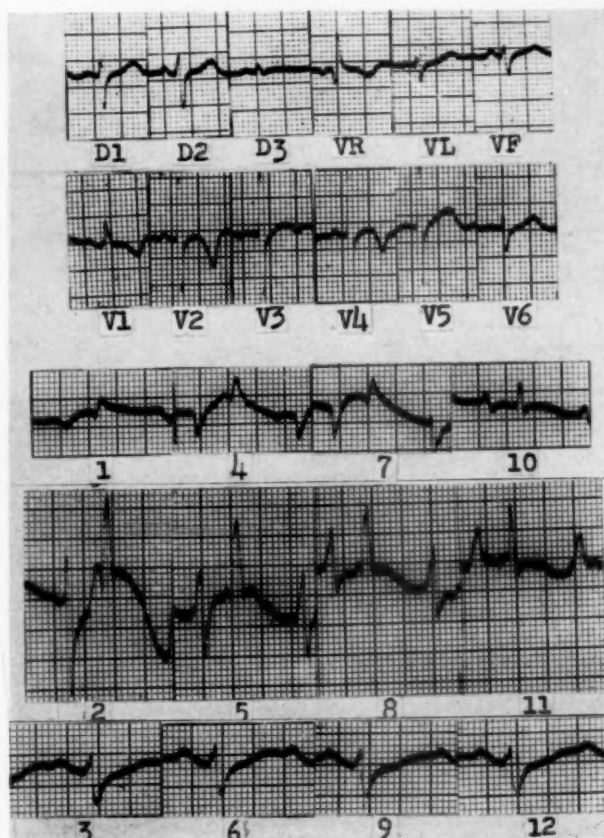


Fig. 1.—M.G.M., 24 years old, white, male, Brazilian, with a normal heart. A, Epicardial leads obtained at the same points indicated in B. B, Right auricular surface. The numbers indicate the points at which leads were recorded. C, Multiple thoracic leads. The first, second, third, etc., of the horizontal levels correspond, respectively, to the first, second, third, etc., intercostal spaces. RScIR = Right supraclavicular region. LScIR = Left supraclavicular region. RPSpL = Right paraspinal line. RScL = Right scapular line. RPAL = Right posterior axillary line. RMAL = Right mid-axillary line. RAAL = Right anterior axillary line. RML = Right mammary line. RSL = Right sternal line. LSL = Left sternal line. LML = Left mammary line. LAAL = Left anterior axillary line. LMAL = Left mid-axillary line. LPAL = Left posterior axillary line. LScL = Left scapular line. LPSpL = Left paraspinal line. MSpL = Mid-spinal line.



A:



B:

Fig. 2.—A and B. (For legend see page 242.)

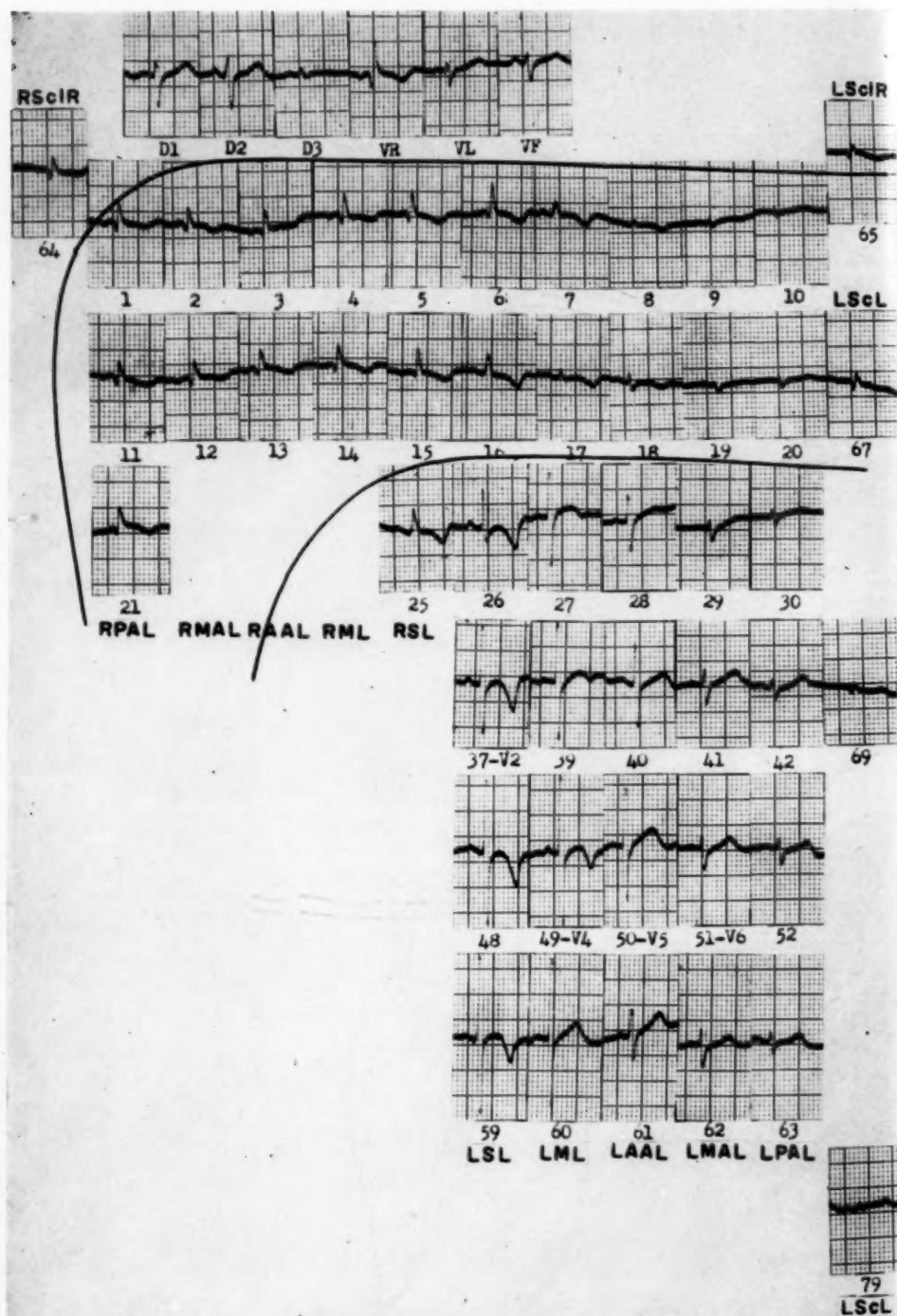


Fig. 2.—J. S., 21 years old, female, Brazilian, with a normal heart. A, Epicardial leads obtained at the same points indicated in B. B, Right auricular surface. The numbers indicate the points at which leads were recorded. C, Multiple thoracic leads. The first, second, third, etc., of the horizontal levels correspond, respectively, to the first, second, third, etc., intercostal spaces. (For key to abbreviations see legend to Fig. 1.)

The same is not true for the P wave. The areas with similar QRS complex morphologies do not necessarily show similar P waves. Therefore, the areas of similar P waves are out of phase with the areas of similar QRS complex.

Some morphologies recorded on the epicardial surface are not recorded on the thoracic surface. Such is the case in normal individuals for P waves with

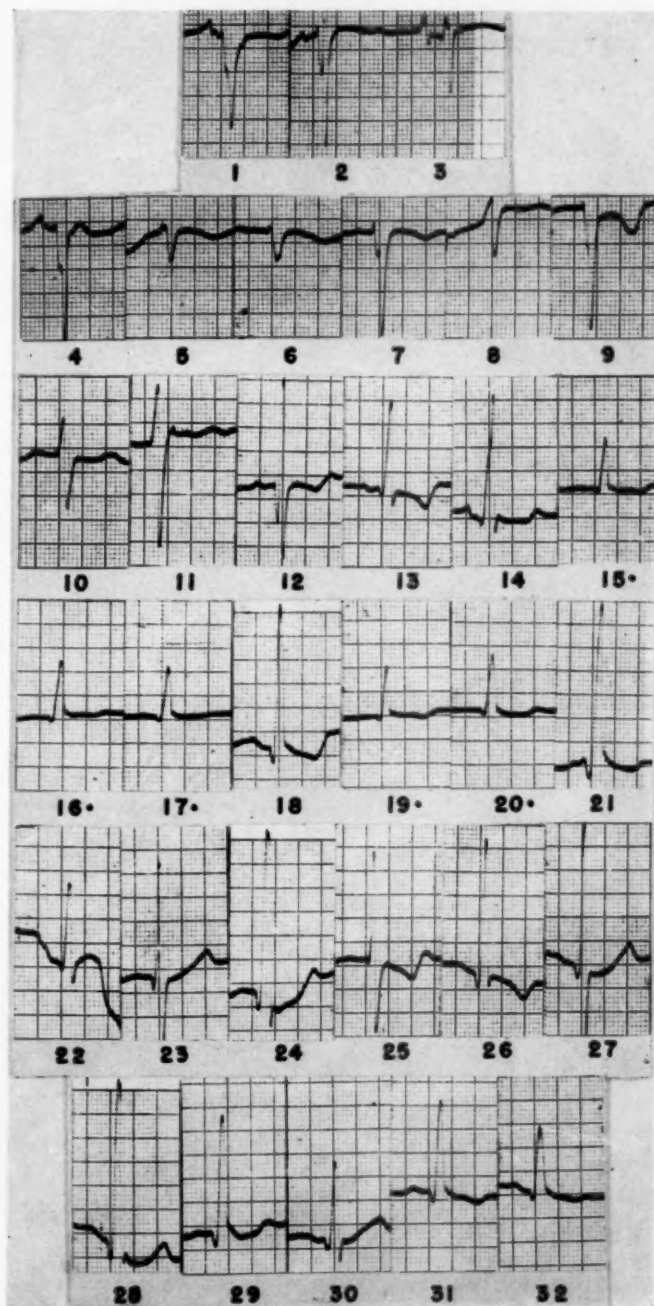


Fig. 3.—A. (For legend see page 244.)

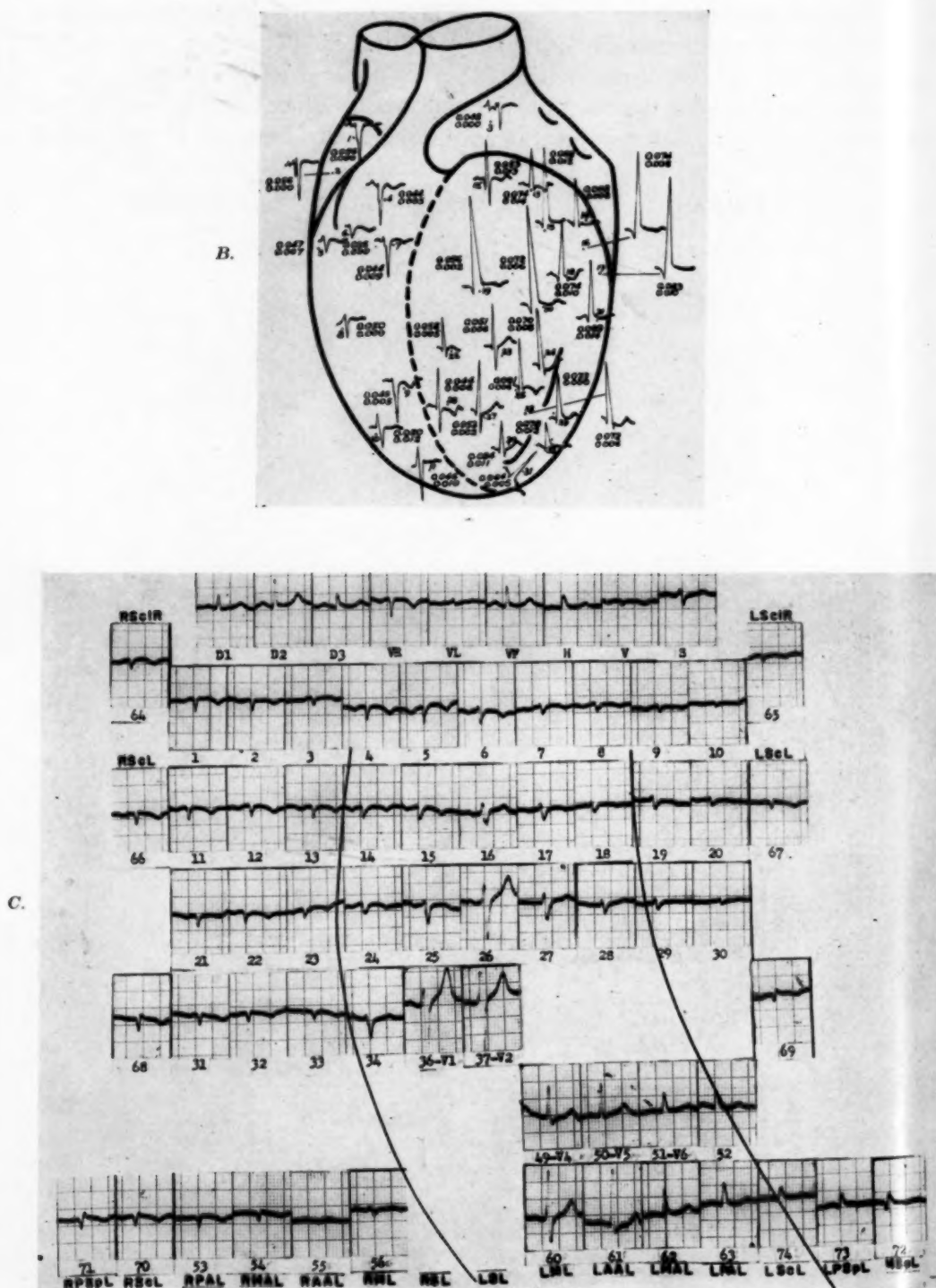


Fig. 3.—A. C., 43 years old, white, male, Polish, with a normal heart. A, Epicardial leads obtained at the same points indicated in B. B, Anterior and lateral ventricular surfaces. C, Multiple thoracic leads. The first, second, third, etc., of the horizontal levels correspond, respectively, to the first, second, third, etc., intercostal spaces. (For key to abbreviations see legend to Fig. 1.)

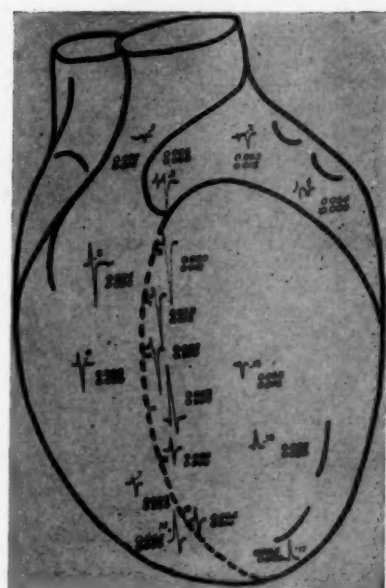
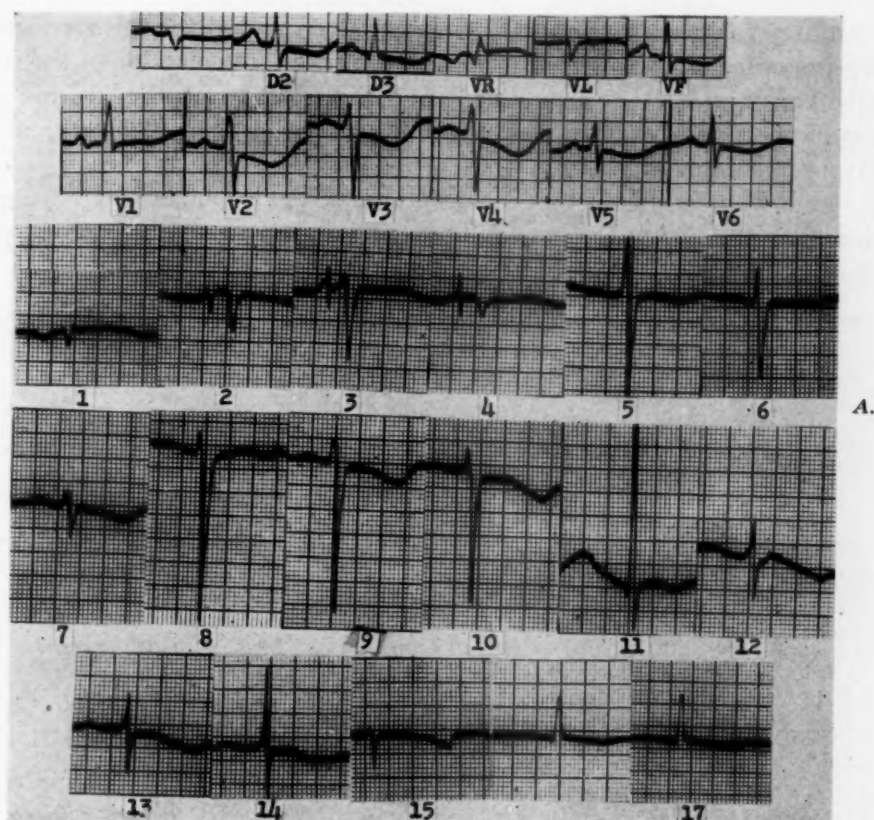
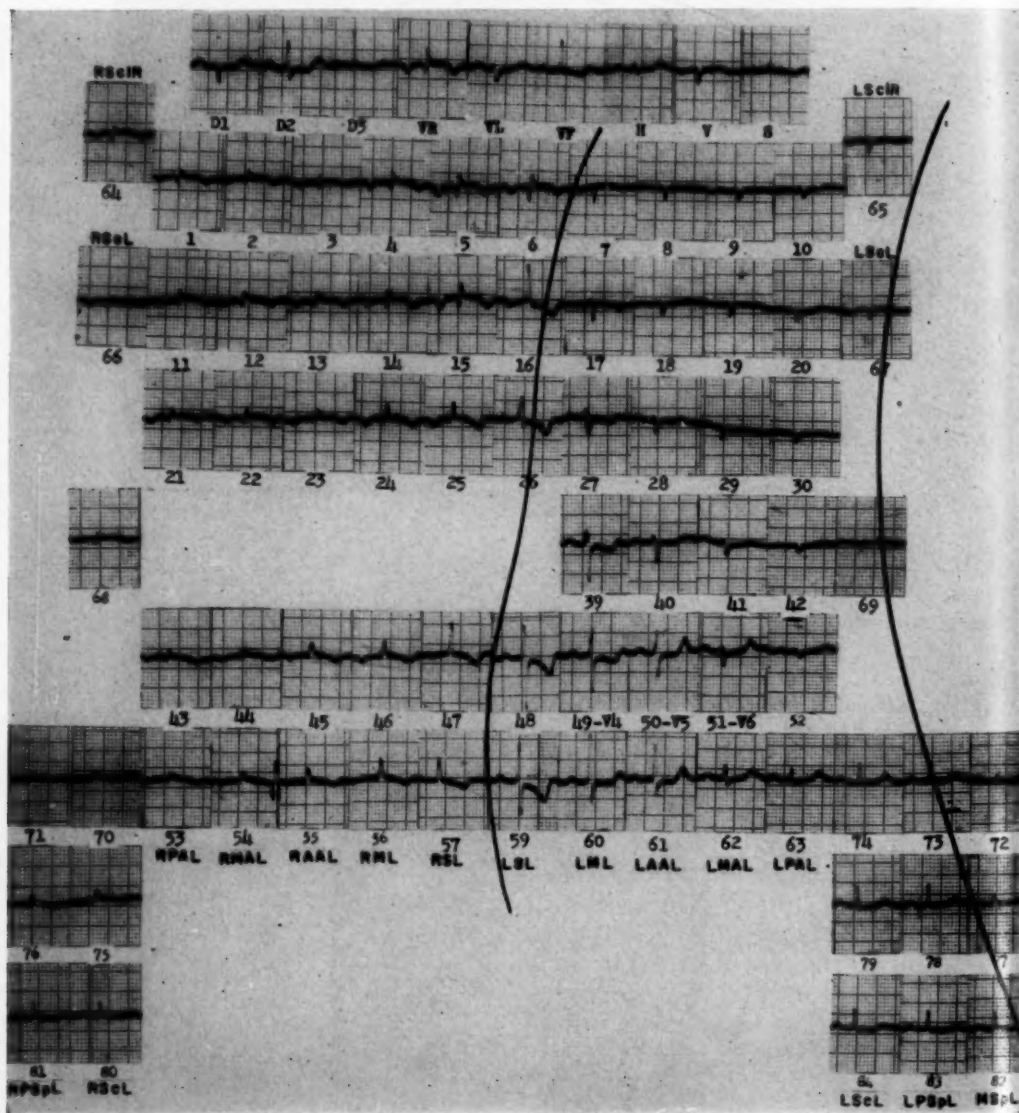


Fig. 4.—A and B. (For legend see page 246.)

small initial negative deflection (qR or qRS patterns) and for QRS complex of QS, QrS (recorded at the highest portion of the anterior projection of the septum and neighboring areas²), and double R and S patterns (recorded in the neighborhood of the right border of the heart, in the highest portion of the anterior and diaphragmatic surfaces²).

It should be pointed out that in normal cases Rs morphologies are frequently recorded near the xiphoid process. They are similar to those recorded on the heart's diaphragmatic surface in its anterior portion.⁴



C.

Fig. 4.—D. M., 23 years old, white, female, Brazilian, with mitral stenosis. A, Epicardial leads obtained at the same points indicated in B. B, Anterior and lateral ventricular surfaces. C, Multiple thoracic leads. The first, second, third, etc., of the horizontal levels correspond, respectively, to the first, second, third, etc., intercostal spaces. (For key to abbreviations see legend to Fig. 1.)

DISCUSSION

The morphologies of the QRS complexes and of the P and T waves, as well as the order in which they follow on the thoracic surface, are similar to those recorded on certain areas of the epicardial surface. Some morphologies of the QRS complex, such as QS and QrS, which are not found on the thoracic surface, can be found in patients with emphysema as well as in those with other conditions simulating myocardial infarction.^{8,9,11}

It should be pointed out that, as Jouve and associates⁷ demonstrated, the same morphologies recorded in the thoracic and epicardial surfaces are not neces-

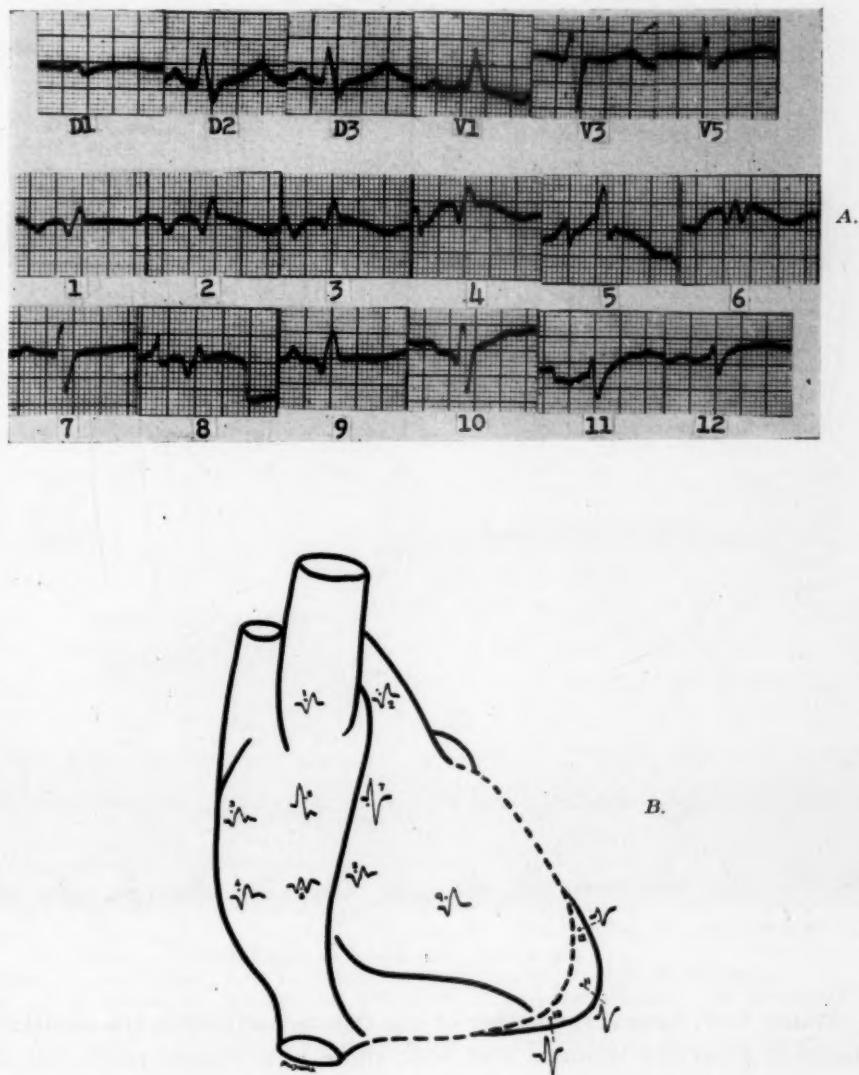


Fig. 5.—Z. F. G., 18 years old, white, female, Brazilian, with right bundle branch block. A, Epicardial leads obtained at the same points indicated in B. B, Anterior and lateral ventricular surfaces. C, Multiple thoracic leads. The first, second, third, etc., of the horizontal levels correspond, respectively, to the first, second, third, etc., intercostal spaces. (For key to abbreviations see legend to Fig. 1.)

At any rate, however, whether or not they are adjacent, the similarity of the patterns of a certain thoracic area with those of a certain epicardial area is of great practical and theoretical importance. It demonstrates, in the first place, that the electrical transmission in the thorax occurs through all the tissues and not preferentially through the muscles. The thorax might be considered, from the practical point of view, as homogeneous, according to Duchosal and Sulzer.⁵

and Jouve and associates.⁶ On the other hand, if one attempts, according to those authors, to explain the findings in the thoracic surface as instantaneous single vectors originating in a single point, the same, with certain limitations,² should apply to the epicardial surface. In the second place, this correlation between both surfaces justifies the opinion held by Sodi-Pallares,¹⁰ as well as many others, as to the reciprocal relationship between certain morphologies and certain heart chambers or zones. This is possible because in the majority of individuals the spread of activation is the same, and therefore the morphologies in the same chambers are similar.

There is no contradiction then between those who interpret the electrocardiographic tracings on a topographic basis and those who interpret them on a vectorial basis. The mentioned correlations are no proof for the validity of the theory of local potential. Such correlations do not necessarily mean that there is a greater or lesser influence of the subjacent myocardium on a certain point of the epicardial surface, but only that both thoracic and epicardial points are liable to the same variations in potential during the cardiac activity.

SUMMARY

During thoracotomy for pulmonary and cardiac diseases (either acquired or congenital) direct epicardial and multiple thoracic leads were recorded in 56 patients, 28 of whom had normal hearts and the other 28 of whom had either single or combined right and left ventricular hypertrophy.

A correlation is shown between the recorded thoracic and epicardial morphologies, although the areas of similar morphologies may not be anatomically adjacent.

The fact that a certain thoracic morphology can be correlated to a certain area in the heart is of practical value, but it does not necessarily mean that there is a greater or lesser influence of the subjacent myocardium on a certain point of the epicardial surface; rather, it means only that both thoracic and epicardial points are liable to the same variations in potential during the cardiac activity.

REFERENCES

1. Barbato, E.: Estudo eletrocardiográfico da ativação ventricular normal e patológica, Tese, Fac. de Medicina, Universidade de São Paulo, 1952.
2. Barbato, E., Pileggi, F., Debes, A. C., Fujioka, T., Magalhães, M. S., Tranchesi, J., San Juan, E., and Décourt, L. V.: *AM. HEART J.* 55:867, 1958.
3. Barbato, E., Fujioka, T., Debes, A. C., Pileggi, F., Bourroul Filho, C., Paula e Silva, P., and Décourt, L. V.: *AM. HEART J.* 56:340, 1958.
4. Barbato, E., Debes, A. C., Pileggi, F., Fujioka, T., Paula e Silva, P., and Décourt, L. V.: *AM. HEART J.* 57:263, 1959.
5. Duchosal, P., and Sulzer, R.: *La Vectocardiographie*, Basel, 1959, S. Karger.
6. Jouve, A., Bouisson, P., Albouy, A., Velasque, P., and Bergier, G.: *La vectographie en clinique*, Paris, 1950, Masson et Cie.
7. Jouve, A., Corriol, J., Velasque, P., Benyammine, R., and Peytavy, R.: *Cardiologia* 33:45, 1958.
8. Myers, G. B.: *Circulation* 1:844, 1950.
9. Myers, G. B.: *Circulation* 1:860, 1950.
10. Sodi-Pallares, D.: *New Bases of Electrocardiography*, St. Louis, 1956, The C. V. Mosby Company.
11. Surawicz, B., Van Horne, R. G., Urbach, J. R., and Bellet, S.: *Circulation* 12:397, 1955.

Case Reports

On a Variety of the "Corrected" Type of Transposition of the Great Vessels Associated With Dextrocardia. A Study of Two Cases With Autopsy Report

Jorge Espino-Vela, M.D., Bolivar Portillo, M.D.,** Guillermo Anselmi, M.D.,**
María V. de la Cruz, M.D.,*** and Michel Reinhold, M.D.,**** Mexico, D.F.*

In the malformation known as transposition of the great vessels the aorta arises from the anatomically right ventricle; it runs parallel and ventral to the trunk of the pulmonary artery, which in turn arises behind the aorta from the anatomically left ventricle (Fig. 1,B). In corrected transposition of the great vessels this abnormal relationship between the ventricles and the great vessels remains unchanged, but the auricles connect with the "wrong" ventricles.¹ In other words, the venous auricle (that which receives the blood from the two venae cavae) connects with the anatomically left ventricle, and the arterial auricle (that which receives the four pulmonary veins) connects with the anatomically right ventricle (Fig. 2,A and B).

The ordinary type of transposition of the great vessels gives rise to a complex physiopathologic picture and a severe clinical condition with marked cyanosis. The reason for this is that the arterial blood enters the left auricle, proceeds to the left ventricle, and through the transposed pulmonary artery recirculates in the lungs. On the other hand, venous blood enters the right auricle and the right ventricle and recirculates through the systemic circuit via the transposed aorta.⁵

On the contrary, the corrected type of transposition of the great vessels is allegedly reported to be a condition compatible with a normal physiologic cardio-

Received for publication April 30, 1959.

*Chief of the Department of Congenital Heart Disease, Instituto Nacional de Cardiología, Mexico.

**Fellows, Instituto Nacional de Cardiología.

***Chief of the Department of Embryology, Instituto Nacional de Cardiología.

****Resident, Instituto Nacional de Cardiología.

vascular hemodynamic pattern since the transposition of the great vessels is "corrected" by the simultaneous "wrong" connections of both auricles (Fig. 2, *A* and *B*). In other words, arterial blood enters the anatomically left auricle through the four pulmonary veins; it then enters the anatomically right ventricle but it adequately supplies the systemic circuit through the transposed aorta. Similarly, the venous blood enters the anatomically right auricle by way of the two venae cavae; it proceeds to the anatomically left ventricle but it is rightly sent to the lungs by way of the transposed pulmonary artery.

In a case of corrected transposition of the great vessels complicated by mirror-image dextrocardia, the arterial auricle is placed to the right and the venous auricle to the left, as pertains to mirror-image dextrocardia.¹ However, the ventricles connect with the "wrong" auricles. Therefore, the anatomically right ventricle is placed to the right and the anatomically left ventricle is placed to the left. But, as in the ordinary type of transposition of the great vessels, the aorta maintains a ventral position with respect to the pulmonary artery and it arises from the right ventricle (Fig. 2, *B*). Again, the pulmonary artery is placed behind the aorta; it arises from the left ventricle. The abdominal viscerae, like the auricles, are placed in a mirror-image position.

When other malformations coexist with the condition described as corrected transposition of the great vessels, a more complex picture is produced, and one can no longer describe it as a true instance of corrected transposition of the great vessels, since the "correction" is to be regarded primarily as a physiologic phenomenon. This paper deals with two cases which illustrated a large number of malformations and had the following features in common: (1) The heart was placed in the right hemithorax and the apex of the heart was directed to the right. There was mirror-image dextrocardia (*situs viscerum inversus*) in both cases. (2) The venous auricle, placed to the left, received both venae cavae and connected with the anatomically left ventricle. The arterial auricle, situated to the right, received the four pulmonary veins and connected with the anatomically right ventricle. In other words, the auricles were the only two chambers of the heart which exhibited a mirror-image position. (3) Unlike the auricles, the ventricles were normally placed in relation to each other, that is, the anatomically right ventricle was right and anterior and the anatomically left ventricle was left and posterior. (4) The aorta was transposed, that is, it arose from the right ventricle in front of the crista supraventricularis and followed a course ventral and parallel to that of the trunk of the pulmonary artery. (5) The pulmonary artery arose behind the aorta and behind the crista supraventricularis from the right ventricle in one case and from both ventricles in the other case. It was stenotic in both. (6) Large septal defects were present in both hearts; specifically, there was a complete variety of atrioventricularis communis in the first case and a combination of auricular septal defect and ventricular septal defect in the second case.

Apparently, the dextrocardia, the presence of pulmonary stenosis, and the large septal defects present in both cases were responsible for the great difference between the clinical picture to which these cases gave rise and that presented by an ordinary case of true corrected transposition of the great vessels.

CASE REPORTS

CASE 1.—This 1-year-old boy (ESH-47697) was first discovered to be cyanotic following a lower respiratory infection at the age of 4 months. Cyanosis increased with effort, during crying spells, and after meals. The patient was admitted to the Instituto Nacional de Cardiología

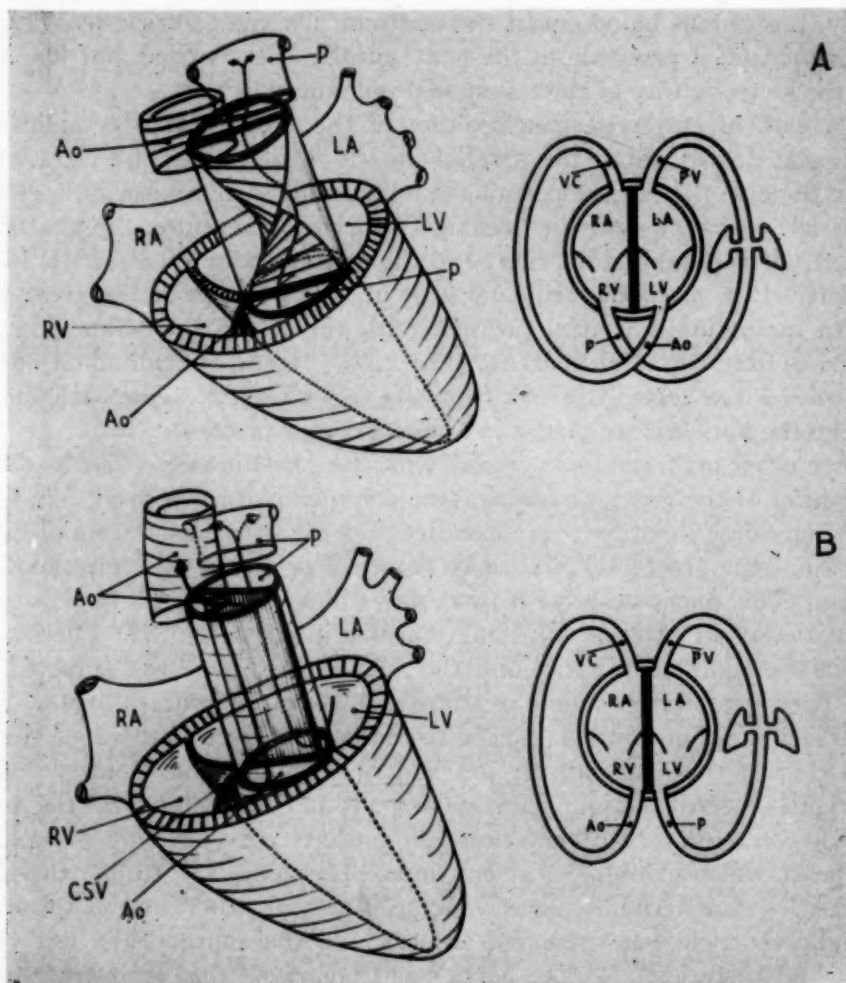


Fig. 1.—In A the diagram at the left depicts the anatomy of a normal heart, with the right chambers on the right side and the left chambers on the left side; the truncus conus exhibits the spiral-shaped septum. The hemodynamic situation is shown at the right. Notice that the great vessels cross each other at their origin. In B the diagram on the left shows the anatomy of a heart with transposition of the great vessels. Notice the straight course of the truncoconal septum. The cardiac chambers are placed normally. To the right is the hemodynamic pattern of this condition, wherein the great vessels arise from the wrong ventricle and do not cross each other. RA: Right auricle. LA: Left auricle. RV: Right ventricle. LV: Left ventricle. CSV: Crista supraventricularis. Ao: Aorta. P: Pulmonary artery. VC: Venae cavae. PV: Pulmonary veins.

in very critical condition with heart failure. Physical examination disclosed a Grade II to III generalized cyanosis and moderate clubbing of the fingers and toes. The heart rate was 160 per minute, and the blood pressure was 90/60 mm. Hg. There was a soft Grade 1 systolic murmur at the second right intercostal space; the second pulmonic sound was not split. The liver was

moderately enlarged and there was a Grade II edema of the lower extremities. The patient was placed on digitalis therapy and dismissed as "improved." He returned a week later with fever and psychomotor excitement. This was soon followed by stupor and vomiting. Physical examination disclosed a positive Brudzinsky sign, right-sided permanent ocular deviation, and right-sided hemiplegia. The pupils were symmetrical and miotic, and the frontal fontanel was tense.

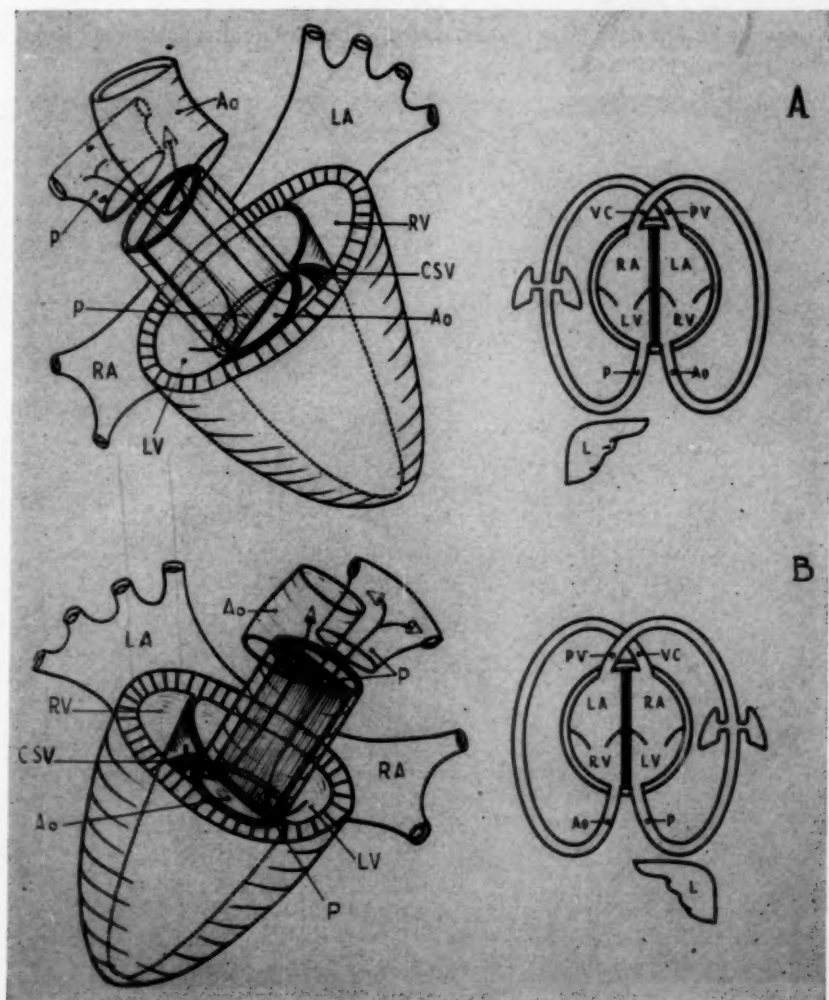


Fig. 2.—Two examples of corrected transposition of the great vessels. In A, a normally placed heart; to the left is depicted the anatomic disposition of the cardiac chambers. Notice that the right auricle (RA) connects with the left ventricle (LV), while the left auricle (LA) connects with the right ventricle (RV) situated to the left. The truncus conus shows a straight septum, whence the aorta springs from the left ventricle, and the pulmonary artery arises from the left ventricle (transposition). To the right is the hemodynamic arrangement of corrected transposition. Notice that the pulmonary artery arises from the left ventricle and enters the lungs, and oxygenated blood returns to the left auricle placed on the left side. The aorta leaves the right ventricle (situated on the left side and its blood returns through the venae cavae (VC) to the right auricle, placed on the right side. While the great vessels run parallel to each other in their origin, the venae cavae and the pulmonary veins (PV) "cross" each other, thus correcting the transposition of the great vessels. The liver (L) is placed normally on the right side, the same side as the right auricle. In B the diagram on the left shows the anatomic disposition in a case in which corrected transposition of the great vessels is associated with dextrocardia; to the right is shown the hemodynamic arrangement of this condition. Here, the ventricles are normally placed, while the auricles and the liver have a reverse position.

The neurological diagnosis was: increased intracranial pressure, hemiplegia, and cerebral lesion located in the posterior fossa affecting the left protuberantial tegmentum. On examination of the blood there were 5,700,000 red cells, 17,000 leukocytes with 78 neutrophils, 14 lymphocytes, and 5 monocytes per cubic millimeter, a hemoglobin of 15 grams per cent, and a hematocrit of 50. On chest x-ray there was a slightly enlarged heart with its apex directed to the right. The right middle arch was concave and the lung fields had decreased vascularity. It was thought that the right ventricle was moderately enlarged. The abdominal viscerae were reversed.

The patient died a few days later in deep coma. The cardiac diagnosis was "possible single ventricle with pulmonary stenosis."

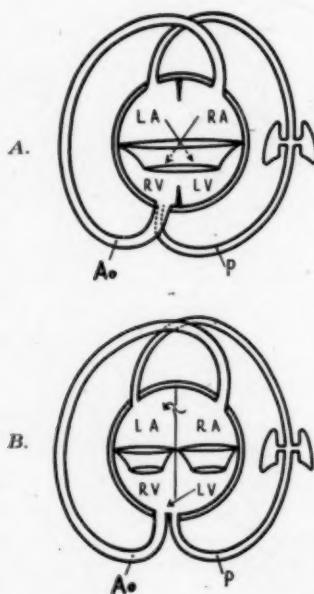


Fig. 3.—The anatomicophysiology of the specimens discussed. Notice that the ventricles are normally placed, while the auricles are in a reverse position. In A there is pulmonary stenosis and an atrioventricularis communis. In B there is also pulmonary stenosis and both auricular and ventricular septal defects. Both cases show that the great vessels run parallel to each other (transposition).

Autopsy Findings.—The cardiac apex was directed to the right. The auricle located on the right side had anatomic features of the left auricle: its walls were trabeculated; it received the four pulmonary veins. The auricle located on the left side showed the limbus of the fossa ovalis. It received the two venae cavae and exhibited the crista terminalis. These features normally belong to the right auricle. The ventricle situated on the right side had the usual anatomic features of a right ventricle, such as the crista supraventricularis. The ventricle situated on the left side was anatomically a left ventricle. Both great vessels emerged from the right ventricle in a parallel fashion, the ascending aorta arose in front of the crista supraventricularis, and the pulmonary artery arose behind this structure. There was pulmonary stenosis of the valvular type. The pulmonary artery trunk was hypoplastic, while the main branches of the pulmonary artery were nearly normal in caliber; the pulmonary valve was bicuspid. The aortic arch descended on the right side. There was a large defect at the lower end of the atrial septum and another one at the basal portion of the ventricular septum, with a single mitrotricuspid ring; an atrioventricularis communis. The liver was in a medial position, its larger lobe being on the left side and its smaller lobe on the right side. The gall bladder was on the left side. The right lung had two lobes; the left one had three lobes (see Figs. 3, A and 4). The anatomic diagnosis was: "corrected transposition" of the great vessels with mirror-image dextrocardia, lateral position of the pul-

monary artery (dextroposition) with unequal partitioning of the truncus conus at the expense of the pulmonary artery, bicuspid pulmonary valve, persistent common atrioventricular canal, right aortic arch, and situs viscerum inversus.

CASE 2.—This 15-month-old boy (JAL-54767) had been cyanotic since birth. He suffered repeated anoxic spells, with increased cyanosis and dyspnea. These spells often ended in convulsive seizures of short duration. Physical examination disclosed a moderately cyanotic child. The apex beat was felt at the fourth right intercostal space about 5 cm. from the midline. A harsh systolic murmur was audible over the entire precordial area. Clubbing of the fingers and

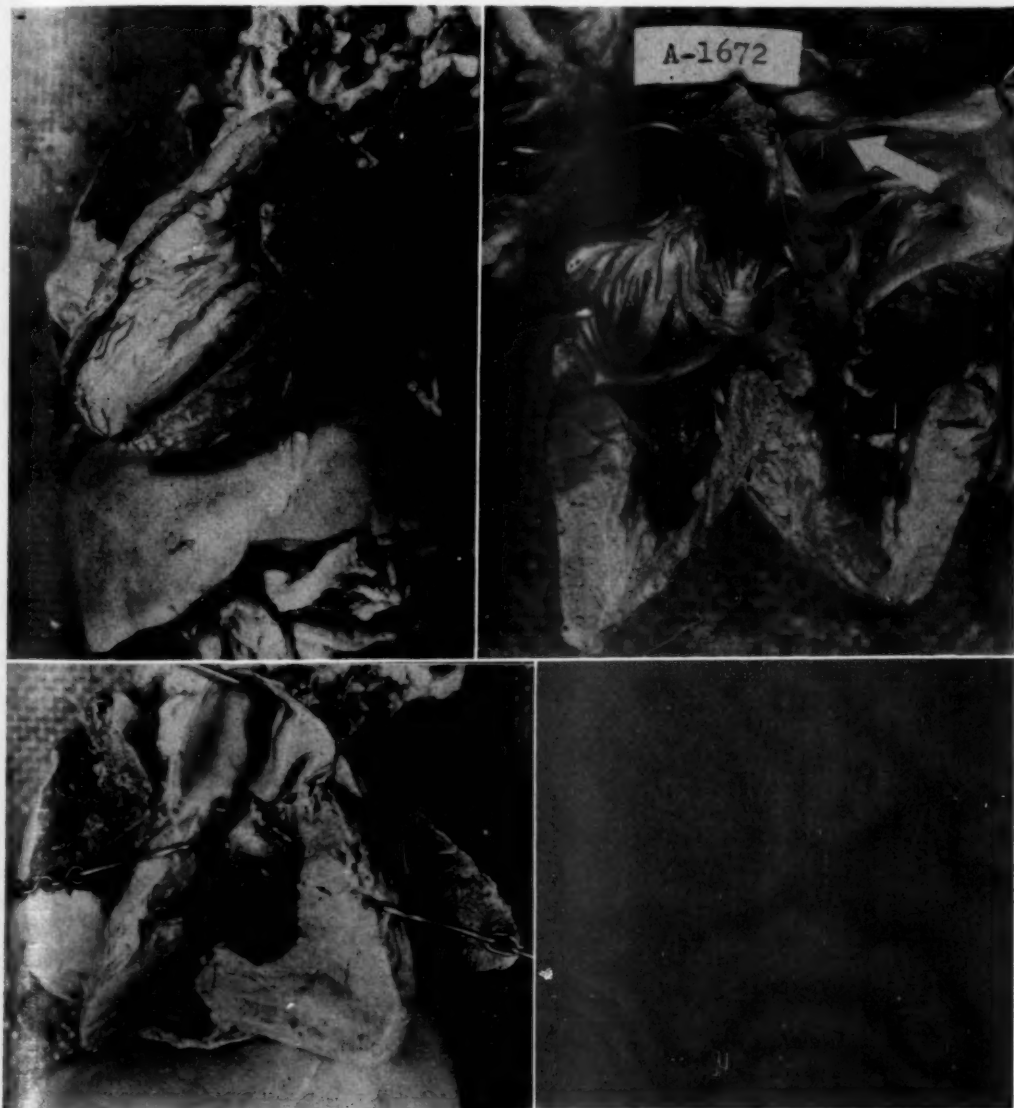


Fig. 4.—Upper left figure shows the heart of Case 1 in place. Notice the apex directed to the right, the ventral position of the aorta, and the left-sided gall bladder. The upper right figure shows the anatomically right auricle situated on the left side; it receives the superior vena cava (indicated by the arrow). Notice also the common atrioventricular canal. The bottom figure shows the anatomically right ventricle on the right side. Notice the large crista supraventricularis; the aorta arises in front of this structure.

toes was present. Blood pressure was 80/50 mm. Hg. X-ray examination disclosed a small heart directed to the right. The lung fields were poorly vascularized. The "pulmonary" segment was concave. The right ventricle was thought to be enlarged. The diagnosis was: dextrocardia with situs viscerum inversus, probable tetralogy of Fallot.

Because it was thought that the patient should be operated upon in order to improve his poor pulmonary circulation, he underwent a Pott's type of anastomosis. The operation was poorly tolerated, and he died the following day.

Autopsy Findings.—The cardiac apex was directed to the right. The auricle situated on the right side received the four pulmonary veins. There was a widely patent foramen ovale. The auricle situated on the left side exhibited the crista terminalis and the limbus fossae ovalis. This chamber received the two venae cavae. All of these features belong to the anatomically right auricle. The ventricle situated on the right side was the anatomically right ventricle. The ascending aorta emerged from this chamber in front of the crista supraventricularis. The pulmonary artery arose behind the crista supraventricularis and behind the aorta, and overrode the ventricular septum. The ventricle located on the left side was anatomically the left one. The ventricular septum exhibited a medial basal defect. The pulmonary valve was stenotic and bicuspid. The great vessels ran parallel to each other, the ascending aorta being ventral to the pulmonary artery. The pulmonary artery trunk was hypoplastic. The right branch of the pulmonary artery exhibited a distal narrowing. The aortic arch descended on the right side. There was situs viscerum inversus. The anatomic diagnosis was: "corrected transposition" of the great vessels with mirror-image dextrocardia, lateral position of the pulmonary artery, unequal partitioning of the truncus conus at the expense of the pulmonary artery, bicuspid pulmonary valve, patent foramen ovale, ventricular septal defect, and situs viscerum inversus (Figs. 3, B and 5).

DISCUSSION

Embryology and Anatomy.—The developmental disorders occurred (1) on the bulboventricular loop, (2) on the truncus conus, and (3) on the atrial and ventricular septa.

1. *Developmental disorders of the bulboventricular loop:* Due to the fact that the auricles are normally the "anchored" portions of the heart, any originally abnormal position of these structures is maintained throughout the development of the heart, regardless of the direction or manner of torsion of the bulboventricular loop. The cases reported here had mirror-image dextrocardia, for which reason their right auricle was on the left side and their left auricle was on the right side. Despite the mirror-image position of the auricles, it is apparent that the bulboventricular loop by means of a right-sided torsion developed toward the right instead of the left side, giving rise to a right-sided convexity and a left-sided concavity; this in turn is the reason for the location of the anatomically right ventricle on the right side. Finally, the apex of the heart was directed to the right side because the heart failed to swing to the left as was to be expected for this type of bulboventricular loop¹ (Fig. 2, B).

2. *Developmental disorder of the truncus conus:* The truncoconal septum normally develops as a spiral structure which divides the truncus conus into two vessels which ultimately show also a spiral course and intertwine around each other² (Fig. 1, A). For this reason, in a normal heart the pulmonary artery is ventral to the aorta at its lower end, where it connects with the right ventricle, and the aorta is dorsal to the pulmonary artery at its origin, where it connects with the left ventricle. In the case of transposition of the great vessels the truncoconal septum does not develop in a spiral fashion. It follows a straight course,³

hence the reversed situation of the lower ends of both vessels and their abnormal origin, that is, the aorta arising as an anterior or ventral vessel from the right ventricle and the pulmonary artery arising in a posterior or dorsal position from the left ventricle. The vessels are therefore parallel to each other (Fig. 1,B).

In the cases under discussion a further disorder of the primitive truncus conus took place, that is, an unequal partition of the truncus conus at the expense of the pulmonary artery. As a result of this the pulmonary artery was very narrow. Finally, a third developmental disorder of the truncus conus was present in these hearts: the normal shifting process of the truncus conus from the right to the left was not complete. Because of this developmental disorder



Fig. 5.—The upper left figure shows the heart of Case 2 in place. Notice the left-sided gall bladder indicated by the arrow. The upper right figure shows the anterior position of the aorta in relation to the narrow, dorsally placed pulmonary artery, indicated by the arrow. The lower left figure shows the anatomically right auricle placed to the left; the probe indicates that the inferior vena cava empties into this chamber. The lower right figure shows the anatomically right ventricle situated on the right side. Notice the anterior aorta, arising in front of the crista supraventricularis. The ventricular septal defect is seen to the left of the septal leaflet of the tricuspid valve.

the pulmonary artery emerged from the right ventricle in one case while it overrode the ventricular septum in the other.⁴ However, the basic reciprocal relationship of the great vessels, that is, transposition, remained unchanged.

In summary, the developmental disorders of the truncus conus were three-fold: (1) transposition, that is, a straight development of the truncocoanal septum; (2) unequal partition of the truncus conus at the expense of the pulmonary artery, causing a narrow pulmonary artery; and (3) dextroposition of the pulmonary artery due to the arrest of the shifting process of the truncus conus from right to left.

3. *Developmental disorders of the auricular and ventricular septa and of the atrioventricular canal:* In one specimen (Case 1) the arrested development of the lower part of the atrial septal complex gave rise to the abnormal persistence of the ostium primum. The ventricular septal defect and the single mitrotricuspid ring (atrioventricularis communis) were produced because of the absence of the endocardial cushions of the atrioventricular canal. In the other specimen (Case 2) a wide patency of the foramen ovale was present. At the ventricular level an independent ventricular septal defect was present also because of the lack of alignment of the conal portion of the truncocoanal septum with the muscular portion of the ventricular septum. The ventricular septal defect was, therefore, the consequence of the lateroposition (dextroposition) of the pulmonary artery. The final arrangement of the anatomy of these hearts is depicted in Fig. 3.

Clinically, the diagnosis was incomplete in both cases because several anatomic features of the malformation were not suspected. Conversely, the diagnoses were partly correct: in both instances the diagnosis of a mirror-image dextrocardia was established, but the exact reciprocal relationship between the auricles and the ventricles was not ascertained. Pulmonic stenosis was correctly suspected, a diagnosis based on the appearance of early cyanosis, dyspnea, and the occurrence of anoxic spells. Another prominent physical finding which also supported the diagnosis of pulmonary stenosis was the presence of a "pure" second pulmonary sound. It was thought that one case had a tetralogy of Fallot with mirror-image dextrocardia, and that the other case had either a single ventricle or a tetralogy of Fallot associated with a mirror-image dextrocardia. The radiologic data supported the diagnosis of dextrocardia and decreased pulmonary flow in both cases.

Electrocardiography.—A retrospective analysis of the electrocardiogram indicates that the diagnosis of dextrocardia was possible and also that the reversed position of the ventricles could have been discovered.

The position of the auricles: A negative P wave in Leads I and aVL (Fig. 6) in the absence of rhythm disorders indicated that the general direction of the auricular activation was from left to right.⁶ In other words, the sinus node was placed in the left-sided auricle, which at autopsy proved to be the venous auricle in both cases, the one in which the node of Keith and Flack is located. This is consistent with the diagnosis of mirror-image dextrocardia. Another useful indication of this diagnosis is the progressively lower voltage of the P wave in the left precordial leads from V₁ to V₆ and a more negative voltage of this wave

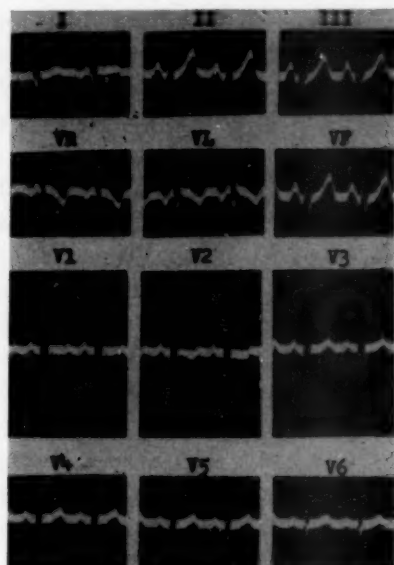


Fig. 6.—Electrocardiogram of Case 2. The P wave is negative in Leads I and aVL; it is more negative in the latter lead than in aVR. The ventricular complex shows ample diphasic deflections in Leads V₁, V₂, and V₃, indicating right septal hypertrophy of the heart. The complexes in V₆ are indicative of variations in potential of the left ventricular wall, in view of the presence of a slurred s wave. For further explanation see the text.

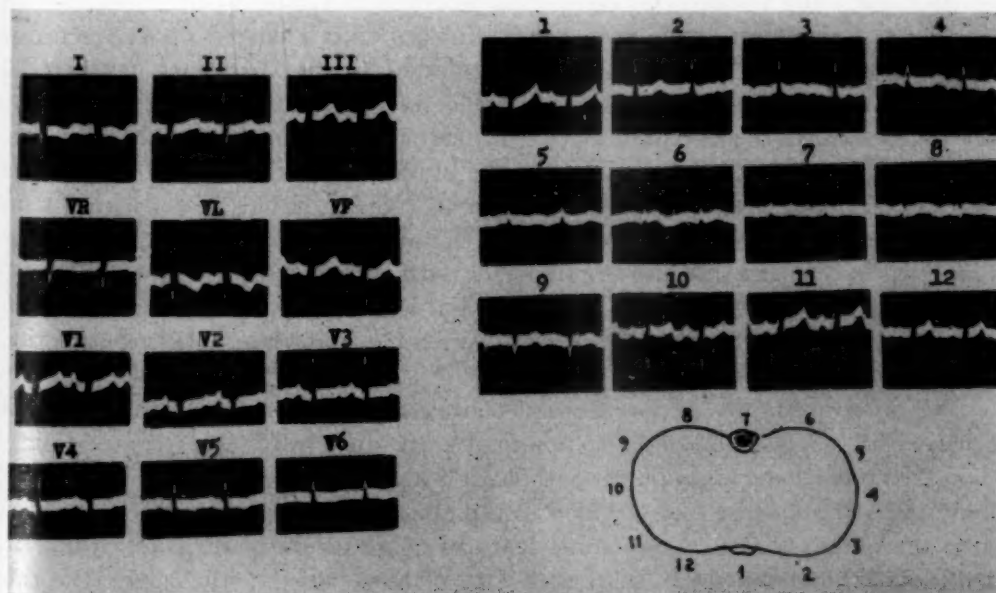


Fig. 7.—Electrocardiogram of Case 1. As in Case 2 the P wave is negative in Leads I and aVL; it is of greater negativity in aVL than in aVR. These findings are consistent with mirror-image position of the auricles. As concerns the ventricular complexes, the qR morphology corresponds to left ventricular variations in potential. This indicates that the left ventricle is placed on the left side, a situation opposite to that of the auricles. The rS morphology of the ventricular complexes in points 9 to 12 of the thoracic circle correspond to the variations in potential of the right ventricle.

in Lead aVL than in Lead aVR. While a negative P wave in the left precordial leads as in Case 2 (Fig. 6) is not the most characteristic feature of mirror-image position of the auricles, its positivity in these cases may be interpreted as being due to the presence of associated right auricular hypertrophy which was apparent in both patients.

The position of the ventricles: Conversely, the morphology of the ventricular complexes indicated that the ventricles were normally located in relation to each other, the left one being placed to the left and the right one to the right. In other words, the position of the ventricles, in contrast to that of the auricles, was not consistent with the diagnosis of mirror-image dextrocardia.

Case 1 showed essentially positive ventricular complexes of the qR type from the left precordial leads V_2 to V_6 , suggesting that left ventricular potential was being recorded from the left side of the chest. Complexes of the rS type which were registered at points 9, 10, and 11 of a thoracic circle (Fig. 7) belong to the trabecular portions of the right ventricle. Finally, isodiphasic complexes of the RS type which were registered at points 12 and V_1 probably correspond to hypertrophy of the right portion of the ventricular septum. The tracing is suggestive of left ventricular hypertrophy in view of an axis of QRS at 0° and a marked counterclockwise rotation of the heart, an idea supported by the fact that left ventricular complexes are registered from Leads V_2 to V_6 and from points 1 to 7 in the thoracic circle. The RS morphology of the ventricular complexes in points V_1 and 2 are suggestive of the possibility of associated right ventricular enlargement.

In Case 2 the transitional complexes recorded in Leads V_1 to V_3 suggest an enlarged right ventricle. The small rs complexes with a slurred s wave recorded in the left precordial leads V_5 and V_6 correspond to the variations in electrical potential of the left ventricle in the presence of right ventricular hypertrophy.

In summary, the common electrocardiographic features of both cases are: (1) The negative auricular P wave in the standard Lead I indicated that the auricular activation was directed from left to right, a situation consistent with the diagnosis of mirror-image position of the auricles. (2) The qR ventricular complexes in one case and the rs complexes with slurred s wave in the other case which were registered over the left precordial leads indicated that the left ventricle was left-sided and that the right ventricle was right-sided, a situation opposite to that of the auricles.

While it is readily apparent that neither case was correctly diagnosed, it seems worth while to discuss the practical consequences of the erroneous diagnoses. In Case 2 the main physiopathologic features were a large venous-arterial shunt and a diminished flow of blood to the lungs. These two conditions happen to be the outstanding hemodynamic features of a case with tetralogy of Fallot. It follows that, independent of the severity of these basic disturbances, the one feature distinguishing this case from one of tetralogy was the altered reciprocal relationship of the great vessels (transposition). We believe that this is of secondary importance in the production of the clinical picture because, theoretically at least, it seems to make little difference whether the pulmonary artery (a stenotic vessel in the case under discussion and also in tetralogy) arises in front of

or behind the crista supraventricularis and the dextroposed aorta. Moreover, because of the "corrected" type of transposition of the great vessels, the transposed aorta in this case was bound to receive a certain amount of arterial blood from the arterial auricle (see Fig. 2,B). However, our case was cyanotic partly because of the presence of large septal defects and partly because of pulmonary stenosis. In particular, in this case the ventricular septal defect in combination with the pulmonary stenosis apparently acted somewhat as do the ventricular septal defect and the pulmonary stenosis of tetralogy of Fallot. This patient died soon after the completion of the operation. The autopsy showed that although a good anastomosis had been made, the operation was unsuccessful because of the presence of another unique malformation, a congenital stenosis of the right pulmonary artery proximal to the site of the anastomosis. We feel that the anastomosis otherwise would have proved beneficial, inasmuch as an increase in pulmonary blood flow is advantageous in many cyanotic malformations with pulmonary stenosis. It was because of the unsuspected distal stenosis of the pulmonary branch that the operation proved useless.

In Case 1, also, there were large septal defects and pulmonary stenosis to account for the cyanosis. It is possible that an operation for the purpose of increasing the reduced pulmonary blood flow would have afforded some benefit. However, considerable doubt springs from the fact that in this case there was an atrioventricularis communis. This patient died because of the brain abscess.

SUMMARY

Autopsy specimens are studied of two cases in which there was a variety of corrected transposition of the great vessels associated with dextrocardia and auricular and ventricular septal defects.

The embryologic basis of this entity is analyzed and the possibility of diagnosing the altered reciprocal relationship of the heart chambers is discussed on the basis of the electrocardiographic and radiologic findings.

Comments on the surgical treatment of one of the cases are made.

REFERENCES

1. de la Cruz, M. V., Anselmi, G., Cisneros, F., Reinhold, M., Portillo, B., and Espino-Vela, J.: An Embryologic Explanation for the Corrected Transposition of the Great Vessels: Additional Description of the Main Anatomic Features of This Malformation and Its Varieties, *Am. HEART J.* **57**:104, 1959.
2. de la Cruz, M. V., and da Rocha, J. P.: An Ontogenic Theory for the Explanation of Congenital Malformations Involving the Truncus and Conus, *Am. HEART J.* **51**:782, 1956.
3. de la Cruz, M. V., and da Rocha, J. P.: Analisis embriológico de la tetralogía de Fallot, del complejo de Eisenmenger y de la transposición de los grandes vasos, *Arch. Inst. cardiol. México* **25**:699, 1955.
4. de la Cruz, M. V., Espino-Vela, J., and Fiamberti, P.: Sobre una variedad de transposición de los grandes vasos, *Arch. Inst. cardiol. México* **27**:703, 1957.
5. Espino-Vela, J., and Quintero, A.: Ventrículo unico asociado a transposición de los grandes vasos. Libro Commemorativo del XXV Aniversario Profesional del Dr. Salvador Aceves, México, 1958, Prensa Médica Mexicana.
6. Portillo, B., Anselmi, G., Sodi-Pallares, D., and Medrano, G.: Importance of the Unipolar Leads in the Diagnosis of Dextrocardias, Levocardias, Dextropositions, and Dextro-rotations, *Am. HEART J.* **57**:396, 1959.

Supernormal Phase of A-V Conduction: Report of Two Cases

Sterling Jonas, M.D., New York, N. Y.

Adrian and Lucas¹ observed in the nerve a critical period following the conduction of an impulse during which a subthreshold impulse was conducted. In addition, impulses of fixed amplitude were transmitted more rapidly than those occurring before or after this phase. This apparently paradoxical phenomenon was subsequently demonstrated in the frog heart and ascribed to a supernormal phase of excitability and conductivity.² Ashman's work^{3,4} on the compressed auricular muscle of the turtle heart added supportive evidence to the view that a supernormal phase of recovery occurs in conduction in diseased or injured tissue. More recently, since the modification of the calibrated oscilloscope, a phase of supernormality was demonstrated in the dog ventricle, the duration of which varied from 50 to 200 milliseconds. The threshold was reported to be 5 to 15 per cent lower than later in the cycle, with changes in threshold as little as 0.01 to 0.05 milliamperes.⁵ The presence of supernormality in the mammal was further supported by the work of Weidmann⁶ on the single isolated Purkinje fiber of the sheep heart.

The initial report of this phenomenon as interpreted from electrocardiograms recorded in human beings was made by Lewis and Master⁷ in 1924, and subsequently by others.⁸⁻¹⁷ Alternate interpretations, however, have been suggested^{12,18} on a number of occasions.

The purpose of this paper is to present two examples of "unexpected" atrio-ventricular conduction believed to have occurred in the supernormal phase of recovery of the A-V junctional tissues, each of which occurred in a different variety of A-V block.

CASE REPORTS

CASE 1.—F., a 65-year-old white man, was admitted to Maimonides Hospital on Aug. 27, 1957, because of severe anterior chest pain of 3 hours' duration. Examination of the heart revealed the presence of a bradycardia. The electrocardiogram taken on admission (August 27) was consistent with an acute posterior wall infarction and manifested an arrhythmia, as depicted in Fig. 1. It shows a regular atrial rate, the atrial cycles varying from 0.74 to 0.78 second. There is an independent ventricular rhythm, essentially regular, its cycle length varying from 1.40 to 1.44 seconds.

From the Department of Medicine, Maimonides Hospital, and the State University of New York College of Medicine at New York City, Brooklyn, N. Y.

Received for publication April 30, 1959.

It is interrupted on four occasions by premature beats of different configuration (*R6* in Lead I, and *R2*, *R8*, and *R13* in Lead II). The conducted atrial impulses (*P8* in Lead I, and *P1*, *P11*, and *P19* in Lead II) all precede the following (premature, bizarre) ventricular complex by a relatively fixed interval ($P-R = 0.44 \pm$ second) and follow their preceding R waves by an R-P interval varying between 0.06 and 0.14 second (0.09, 0.06, 0.06, and 0.14 second). It should be noted that they are the only P waves which fall into this range. All of the other nonconducted P waves occur either too soon after the preceding R wave (*P17* in Lead II after 0.03 second, and *P25* in Lead II after 0.04 second) or too late ($R-P = 0.26$ second or more).

It appears therefore that we are dealing with A-V dissociation due to a high degree of A-V block, the refractory period being at least that of the R-R interval.

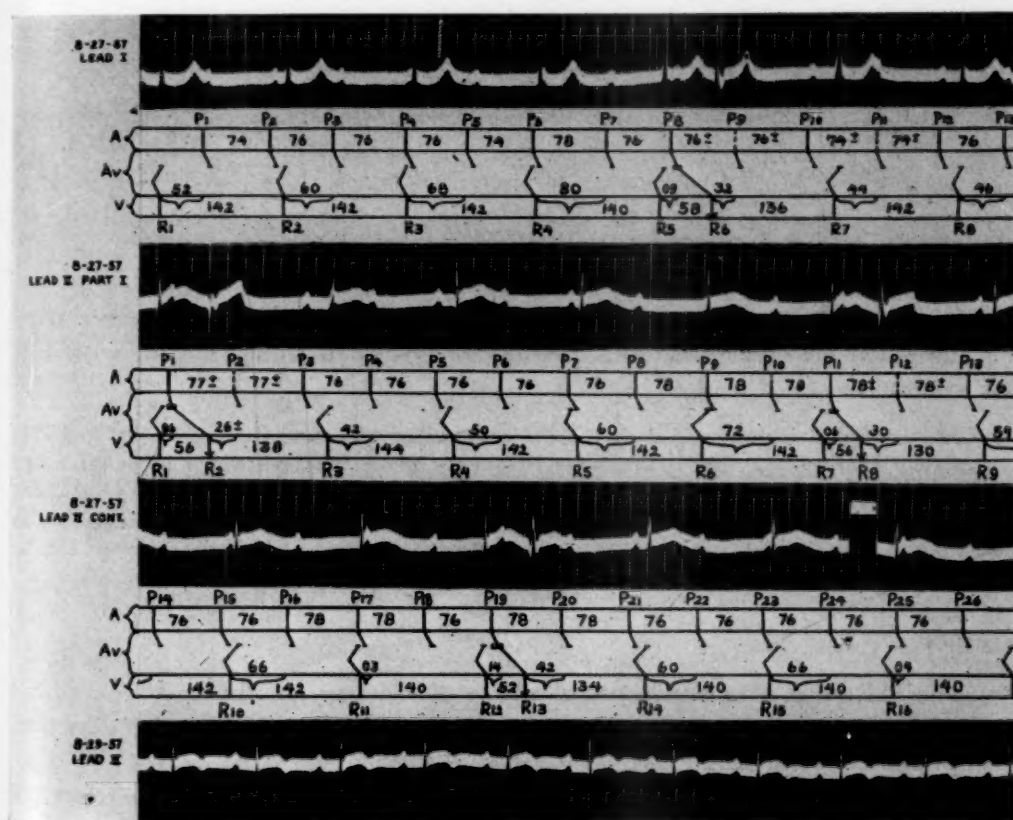


Fig. 1.—Case 1. Lead I (Aug. 27, 1957) shows atrioventricular dissociation. *R6* occurs prematurely after an R-P equal to 0.09 second, and its QRS complex differs slightly from that of the other regular beats. The interventricular distance following the premature beat (*R6-7*) is less than the basic interventricular distance. The atrial beat (*P8*) is represented as manifesting a delay in conduction from the pacemaker level to the ventricle in excess of the antegrade conduction of the following nodal beat. This difference in forward conduction accounts for the relatively short interval (*R6-7*). Lead II (Aug. 27, 1957). Two strips form a continuous tracing. There is, again, atrioventricular dissociation with regular ventricular action, which, however, on three occasions is interrupted by premature beats (*R2*, *R8*, and *R13*). The latter are preceded by R-P intervals ranging from 0.06 to 0.14 second. The premature ventricular beats differ in shape from the regular beats. They are conducted beats which have resulted from the atrial impulses *P1*, *P11*, and *P19*, respectively. The interventricular distances (*R2-3*, *R8-9*, and *R13-14*) following the premature beats are less than the basic interventricular distance. Lead II (Aug. 29, 1957). Regular sinus rhythm with full atrioventricular conduction has returned. The P-R is equal to 0.28 second.

The nodal impulse, in the course of its retrograde passage into the A-V junctional tissue, allows a supernormal phase of recovery to occur at a fixed time interval after the QRS (which has resulted from the more rapid antegrade conduction to the ventricle). The duration of this interval is 0.08 second, as determined from the P waves which fall within the range of conductible impulses. The sinus impulses (*P8* in Lead I, and *P1*, *P11*, and *P19* in Lead II) which reach the junctional tissue during this particular phase are conducted to the ventricle. Because the R-R interval preceding the conducted beat is relatively short, conduction occurs with intraventricular aberration. The R-R intervals following the conducted beats (*R6-7* in Lead I, *R2-3*, *R8-9*, and *R13-14* in Lead II) are somewhat shorter (1.30 to 1.38 seconds) than the other ventricular cycles (1.40 to 1.44 seconds). This is explained by the fact that conduction time from the nodal pacemaker level is longer for premature conducted sinus beats than for the following nodal beats^{19,20} (see Fig. 1).

Analysis of available tracings, including 100 ventricular beats (not represented here), revealed that all conducted impulses occurred at an R-P interval ranging from 0.06 to 0.16 second, and that no atrial impulse falling within this critical period failed to be conducted. Moreover, no atrial beat which occurred less than 0.04 or more than 0.16 second following the R wave was conducted to the ventricle (see Fig. 3).

Another electrocardiogram (Fig. 1) taken on Aug. 29, 1957, two days after the admission electrocardiogram, revealed reversion to sinus rhythm with full A-V conduction (P-R = 0.28 second)

CASE 2.—Fig. 2 represents a sinus rhythm with evidence of a second degree (3:2 and 2:1) A-V block. The sinus rhythm is somewhat irregular. Those P waves which occur relatively early after the preceding R wave (0.60 second or less) are conducted to the ventricle, while other P waves which fall more than 0.60 second after the preceding R wave are not. This suggests the presence of a critical period or supernormal phase of recovery during which the impulses can be conducted to the ventricle.

COMMENT

The existence of a supernormal phase of recovery in the A-V junctional tissues would explain, in the two cases reported here, the paradoxical conduction of impulses not ordinarily expected to be conducted.

Alternate interpretations based on variations in vagal tone, interference phenomenon, and premature ectopic beats have been suggested to explain similar tracings. Variations in vagal tone may be associated with a sinus arrhythmia and varieties of A-V block. The mechanism of interference, as described by Wolferth,²¹ implies "interference" between an atrial and nodal (or ventricular) impulse in the junctional tissue, thus allowing a longer rest period for the subsequent conduction of the next sinus impulse to the ventricle.

In the cases described here, however, it is *not* likely that the foregoing interpretations would explain the phenomenon observed.

In Case 1 the extreme regularity of the atrial rate speaks against a vagal effect. As for interference, the pauses between the nonconducted atrial impulses (*P7* in Lead I, and *P10* and *P18* in Lead II) and the immediately following ven-

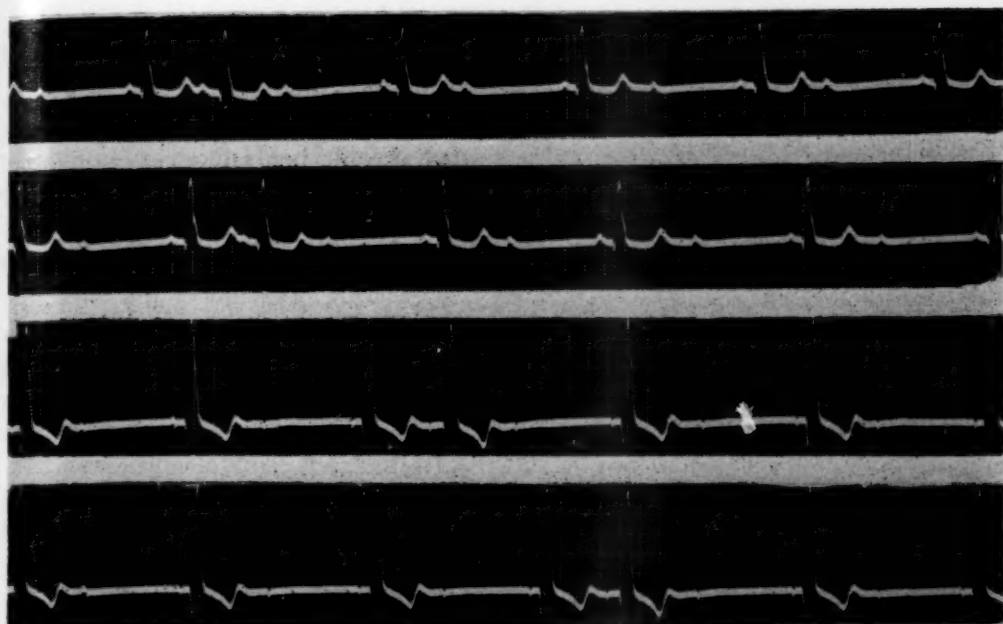


Fig. 2.—Case 2. There is a sinus arrhythmia with 3:2 and 2:1 atrioventricular block. Those P waves which occur less than 0.60 second after the preceding R wave are conducted to the ventricle, whereas those P waves which fall more than 0.60 second after the preceding R wave are not conducted.

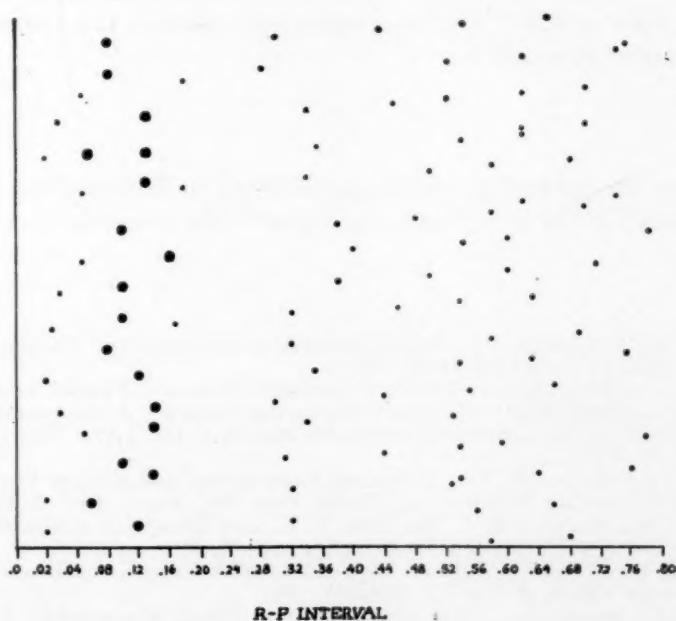


Fig. 3.—Comparison of the R-P intervals of 84 blocked and 18 conducted sinoauricular excitations which follow automatic ventricular beats. All conducted impulses occur after an R-P interval ranging from 0.06 to 0.16 second. ● Atrial excitations conducted to the ventricle. ○ Blocked atrial excitations.

tricular impulses are so long (varying from 0.62 to 0.68 second) that it is unlikely that these beats interfere with each other. Premature ectopic beats would not explain the fact that they are preceded at a rather constant interval (P-R) by a regular sinus excitation—which in turn has a constant time relation to the preceding ventricular beat (R-P). Premature ectopic beats likewise would not explain the relatively short R-R which follows the conducted beats.^{19,20} In three cases reported by Dressler²² a total of sixteen atrial and thirty-four ventricular premature beats were observed in the presence of A-V rhythm. In every instance the returning cycle was noncompensatory, suggesting invasion of the dominant pacemaker. If the prematurely occurring beats represented here were of ectopic origin, and invaded the pacemaker, it would be expected that the succeeding R-R would be more than 1.40 seconds (rather than less). (The explanation for the relatively short R-R has been noted. See Fig. 1.) If the prematurely occurring beats were of nodal origin and manifested delay in the antegrade conduction to the ventricle, this could explain the subsequent short R-R interval. It would not explain, however, the temporal relationship of these premature beats to the preceding atrial and ventricular impulses (see Fig. 3).

In Case 2, although there is a sinus arrhythmia present, the sinus impulses are conducted only when the P waves occur at a critical R-P distance, thus manifesting evidence against a vagotonic effect as the singular explanation. The interference mechanism would not apply in this situation in the absence of A-V dissociation. As for premature ectopic beats, although it is possible to consider the tracing as representing a sinus rhythm with premature supraventricular (atrial) beats, this alone would not explain why those premature atrial beats which follow after a short R-P are conducted, whereas the "premature" atrial beats which occur later are not.

SUMMARY

Two cases are presented which are believed to demonstrate a supernormal phase of recovery in the A-V junctional tissue in the presence of A-V block.

REFERENCES

1. Adrian, E. D., and Lucas, K.: On the Summation of Propagated Disturbances in the Nerve and Muscle, *J. Physiol.* **44**:68, 1912.
2. Adrian, E. D.: The Recovery Process of Excitable Tissues, *J. Physiol.* **54**:1, 1920.
3. Ashman, R.: Conductivity in Compressed Cardiac Muscle. A Supernormal Phase in Conductivity in the Compressed Auricular Muscle of the Turtle Heart, *Am. J. Physiol.* **74**:140, 1925.
4. Ashman, R., and Wooley, E.: Combined Supernormal and Fatigue Phenomena in Compressed Cardiac Muscle of the Turtle, *Proc. Soc. Exper. Biol. & Med.* **23**:159, 1925.
5. Brooks, C. M., Hoffman, B. F., Suckling, E. E., and Orlas, O.: Excitability of the Heart, New York, 1955, Grune & Stratton, Inc., pp. 25, 74.
6. Weidmann, S.: Effects of Calcium Ions and Local Anesthetics on Electrical Properties of Purkinje Fibers, *J. Physiol.* **129**:568, 1955.
7. Lewis, T., and Master, A.: Supernormal Recovery Phases Illustrated by Two Clinical Cases of Heart Block, *Heart* **11**:371, 1924.
8. Ashman, R., and Herrmann, G. R.: A Supernormal Phase in Conduction and a Recovery Curve for the Human Junctional Tissues, *AM. HEART J.* **1**:594, 1926.
9. Burchell, H. B.: Observations on Additional Instances of ANP in the Human Heart, *J. Lab. & Clin. Med.* **28**:7, 1942.

10. Kline, E. M., Conn, J. W., and Rosenbaum, F. F.: Variations in V-A and A-V Conduction Dependent Upon the Time Relations of Auricular and Ventricular Systole: The Supernormal Phase, *AM. HEART J.* **17**:524, 1939.
11. Luten, D., and Pope, S.: Variations in Heart Block Sometimes Attributed to the Supernormal Recovery Phase, *AM. HEART J.* **5**:750, 1930.
12. Mack, I., Langendorf, R., and Katz, L. N.: The Supernormal Phases of Recovery of Conduction in the Human Heart, *AM. HEART J.* **34**:374, 1947.
13. Scherf, D., and Schott, A.: The Supernormal Phases of Recovery in Man, *AM. HEART J.* **17**:357, 1939.
14. Pick, A., and Fishman, A. P.: Observations in Heart Block. Supernormality of A-V and Intraventricular Conduction and Ventricular Parasystole Under the Influence of Epinephrine, *Acta cardiol.* **5**:270, 1950.
15. Segers, M., and Van Dooren, F.: La dissociation A-V avec captures precoces du ventricule. Etude de la phase supernormale de la conduction, *Acta cardiol.* **1**:99, 1946.
16. Wastl, H.: Die übernormale Phase der Erholung des Herzmuskels nach einer Systole, *Ztschr. Biol.* **75**:289, 1922.
17. Katz, L. N., and Pick, A.: Clinical Electrocardiography. Vol. 1, The Arrhythmias, Philadelphia, 1956, Lea & Febiger.
18. Wenckebach, K. F., and Winterberg, H.: Die Unregelmässige Herztätigkeit, Leipzig, 1927, Wilhelm Engelmann, p. 336.
19. Lewis, T., and White, P. D.: The Effect of Premature Contractions in Vagotomized Dogs, With Especial Reference to Atrio-Ventricular Rhythm, *Heart* **5**:335, 1914.
20. Scherf, D.: Reizleitungsstörungen im Bündel. III, Mitt Nachweis einer Leitungsstörung im Bündel an klinischen Fällen, *Wien. Arch. inn. Med.* **12**:327, 1926.
21. Wolferth, C. C.: The So-Called Supernormal Recovery Phase of Conduction in Heart Muscle, *AM. HEART J.* **3**:706, 1928.
22. Dressler, W., and Roesler, H.: Premature Beats in Atrio-Ventricular Rhythm, *AM. HEART J.* **51**:261, 1956.

Review

The Nitrous-Oxide Method for Determining Coronary Blood Flow in Man

George G. Rowe, M.D., Madison, Wis.*

INTRODUCTION

With the establishment of the nitrous-oxide method for determination of cerebral blood flow¹ it was realized that the method should be applicable to any homogeneous organ which was uniformly perfused by blood, and from which a reasonable sample of venous blood could be obtained. The heart and coronary circulation appeared to fulfill these criteria, and the nitrous-oxide method was therefore quickly adapted to the determination of coronary blood flow in the dog²⁻⁴ and in man.⁵ It is the purpose of this paper to review the considerable body of data which has now been accumulated by this method in man, as well as to discuss the method itself.

PRINCIPLE AND EXPERIMENTAL VERIFICATION

The principle of the nitrous-oxide method involves the assumption that a highly diffusible gas will reach equilibrium between the venous blood and the tissue of an organ in a relatively short period of time.¹ If such an equilibrium is reached, and if the partition coefficient between blood and the tissue is known, the amount of gas taken up by the tissue can be calculated. The arteriovenous difference throughout the saturation period can be measured by construction of curves from multiple samples of arterial and venous blood withdrawn during the period of saturation. Then, when it is known how much gas has been taken up by the organ and how much has been extracted from each unit of perfusing blood, flow can be calculated by the use of the Fick principle.⁶

It was shown in experimental animals that equilibrium between the blood of the internal jugular bulb and the brain tissue was reached in about 10 minutes.⁶

Received for publication April 12, 1959.

*Markle Scholar and Associate Professor, Department of Medicine and Cardiovascular Research Laboratory, University of Wisconsin Medical School, Madison, Wis.

Furthermore, the partition coefficient for nitrous oxide between brain and blood was approximately 1.0 by *in vitro* and *in vivo* testing, as well as when calculated empirically by comparing cerebral blood flow measured by the bubble flowmeter and the nitrous-oxide method.⁶ Similar experiments with the bubble flowmeter have, to some extent, validated the nitrous-oxide method of determining coronary blood flow.⁴ Thus, in dogs, the partition coefficient between heart muscle and blood was established for nitrous oxide *in vitro* as 1.05.⁴ Simultaneously, "*in vitro*" experiments with human myocardium established the partition coefficient of 1.13.⁴ However, when comparisons were made between coronary blood flow as measured by the bubble flowmeter and that determined by the nitrous-oxide method, the empirical partition coefficient was 0.97, since the use of this coefficient caused results of the two methods to check more closely than did the higher coefficient.⁴ Comparison of coronary blood flow by the nitrous-oxide method and the rotameter in dogs has shown relatively good agreement, with an average variation between the two of ± 12.4 per cent.⁷ In the human being, in the absence of any other method of determining the coronary blood flow per unit of weight, the "*in vivo*" partition coefficient remains unknown, and opinions are divided as to whether to use the partition coefficient of 1.0 established empirically for the dog "*in vivo*" or 1.1 established "*in vitro*" for human heart muscle.⁴ Since at present there is no unanimity of opinion, it seems best for observers to state which partition coefficient they have used, so that their results may be compared with the work of others. A partition coefficient of 1.1 results in 10 per cent higher calculated coronary flows and myocardial metabolic values than does a coefficient of 1.0.

In the kidney of the dog the partition coefficient between blood and kidney did not change after replacement of portions of the kidney parenchyma by fibrosis secondary to chronic destructive lesions, or after production of an acute diffuse inflammatory process.⁸ Such experiments have not been done with the heart, but, reasoning by analogy from the kidney, it would seem that no particular allowance has to be made for replacement of heart muscle by fibrous tissue, or infiltration by inflammatory exudate. The partition coefficient, however, continues to be one of the assumptions basic to the method and probably will not be clarified further until other methods for determining coronary flow are available for comparison. Although information is not available to prove that it is so, it has been anticipated that since nitrous oxide is relatively more soluble in fat than in muscle,⁹ if the coronary blood is exposed to significant deposits of fat in its passage through the myocardium, the nitrous-oxide uptake would be increased, the arteriovenous nitrous-oxide difference widened, and a slower calculated coronary flow would result. This might explain the very slow flows sometimes recorded in obese subjects.

In the dog, at least, the coronary sinus drains chiefly the left ventricle.¹⁰ Although there is no reason to assume from Gregg's physiologic experiments that the same is true in man, traditionally it has been done because of the anatomic distribution of the arterial and venous channels in the human heart. It does not necessarily follow that venous blood from areas of the heart which do not drain through the coronary sinus has a different concentration of nitrous

oxide, but in order to avoid assumptions as to whether or not it does, coronary flow determined by the nitrous-oxide method is ordinarily expressed in milliliters per 100 grams of left ventricle per minute. It is perhaps fortunate that the use of the method does not depend on drainage of the whole left ventricle through the coronary sinus; all that is required for validity is that the fraction of blood draining through the coronary sinus have the same concentration of nitrous oxide as does the rest of the left ventricular venous blood. With such a highly diffusible gas as nitrous oxide and such extensive anastomoses as are present between the small myocardial vessels,¹¹ this seems to be a reasonable assumption. In the presence of coronary artery disease, as the uniformity of vascularity decreases, the probability of uniform mixing decreases and the reliability of the method seems relatively less. Arteriovenous fistulae from the coronary artery to the coronary veins or to the coronary sinus, or anomalous drainage of veins, such as that of the left superior vena cava into the coronary sinus, by contaminating the myocardial venous specimen, vitiate the method.

Unfortunately, since there is no good method of determining left ventricular weight *in vivo*, and since coronary blood flow is measured per 100 grams of left ventricle, there is no way of measuring actual efficiency in man. Some have calculated efficiency from tables concerning normal heart weight,¹² on the assumption that the left ventricle constitutes 53 per cent of the total heart weight.¹³⁻¹⁵ On this assumption, in those with hypertrophied hearts the calculated efficiency will be misleadingly high.¹⁴ When comparisons are made of cardiac efficiency in the same subject before and after a procedure during the same catheterization, it is reasonable to calculate an index of efficiency which describes the amount of work done per unit of oxygen consumption by each 100 grams of myocardium. Thus, the relative efficiency can be compared quite accurately in the control and experimental periods, since the myocardial weight could not have changed significantly during a relatively short experiment. As the time period between the two studies increases, the validity of even this method of comparison of efficiency becomes progressively less.

TECHNIQUE

The technique of the nitrous-oxide method for determining coronary blood flow requires sampling from a peripheral artery and a cardiac catheter whose tip lies in the coronary sinus. In the anteroposterior projection the catheter position is accepted as being in the coronary sinus when: (1) the distal few centimeters of the catheter tip lie relatively straight and parallel to the expected position of the coronary sulcus^{16,17}; (2) the motion of the straight portion of the catheter tip is obliquely cephalocaudal perpendicular to the axis of this portion of the catheter and parallel to the longitudinal axis of the heart¹⁸; (3) a venous type of pressure curve is obtained through the catheter^{14,16-19}; (4) arrhythmias are very uncommon, even when the catheter is advanced and withdrawn within the coronary sinus¹⁴; (5) blood withdrawn from the catheter is very dark in color and low in oxygen content as compared with the pulmonary arterial specimen^{14,16-19}; (6) attempts at rapid aspiration are met with obstruction of the tip

of the catheter so that blood flow is suddenly checked, apparently by aspiration of the coronary sinus wall or valves into the lumen of the catheter; (7) if the catheter is inadvertently advanced too far, a pressure is recorded which is similar to a somewhat damped arterial curve²⁰ or a ventricular pressure curve which is delayed in onset when compared with the electrocardiographic onset of ventricular systole.^{16,17,19,20} Ordinarily, during deep penetration, blood cannot be aspirated readily. Such deep positioning of the catheter is not advisable anyway, since samples drawn from any position which is clearly inside the sinus were found to be the same,⁴ and deep penetration is more apt to produce complications.

When the catheter is in place and the patient "basal," as determined by observation of the patient, his pulse, respiration, and blood pressure, a mixture of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen is administered throughout a 10-minute period, and multiple samples are drawn from the artery and the coronary sinus.¹⁸ The blood specimens are analyzed for content of nitrous oxide by the method of Orcutt and Waters.²¹ Curves are drawn intercepting the points on the time-concentration scale for the arterial and venous concentrations of nitrous oxide, and the coronary flow is calculated by the Fick principle.^{6,18}

Several workers have used desaturation curves for calculating coronary blood flow.^{22,23} In this case the nitrous oxide is administered for a period of time, usually 12 to 15 minutes, and then, at the onset of the determination of coronary flow the administration of nitrous oxide is terminated and the patient breathes room air. Blood specimens are drawn in the same manner as they are during the determination of flow by saturation with nitrous oxide. The arterial content of nitrous oxide falls rapidly and exponentially, whereas the venous curve falls more slowly. The arterial and venous contents tend to reach the same level at or before 10 minutes. Under these circumstances the myocardial content of nitrous oxide at the beginning of the study (presumed to be the original content of nitrous oxide in the coronary sinus) is divided by the venoarterial nitrous-oxide difference throughout the desaturation period, and flow is calculated, again, by the Fick principle.²² Coronary blood flow as measured by the saturation and desaturation method has been found to be the same.²²

Rather than draw many specimens and construct curves for the content of nitrous oxide in arterial and venous blood, it has been suggested that a specimen be drawn continuously from the arterial and from the venous sides of an organ's circulation throughout the total 10-minute period of saturation. This gives an automatically integrated arterial and venous specimen throughout the period of saturation.²⁴ The final venous level is determined at the end of the period of saturation and is divided by the arteriovenous difference determined from the integrated specimens. Most workers have continued to use the intermittent sampling technique so as to be able to examine the curves, since they believe they then have a better index of the validity of the determination.

Since coronary blood flow and myocardial metabolism are informative chiefly as related to cardiac output and cardiac work, it is important to obtain this information as closely as possible to the time the determination of coronary flow is made. This may be done by moving the cardiac catheter from the pulmonary

artery to the coronary sinus or vice versa between the determinations of cardiac output and coronary flow. In five control subjects in whom this method was used, satisfactory agreement between the first and second studies was obtained.²⁵ On the other hand, two cardiac catheters may be used simultaneously, placing one in the pulmonary artery and the other in the coronary sinus.²⁶ Two catheters have been used without difficulty unless the vein is small, in which case venous spasm may make manipulation of the catheters difficult.

Several criteria are used to judge the acceptability of a determination of coronary flow: (1) The cardiac catheter tip must lie in a position which is accepted radiographically as being in the coronary sinus. (2) Blood aspirated from the coronary sinus must be low in oxygen content as compared to that from the pulmonary artery, indicating that an uncontaminated specimen of coronary sinus blood has been obtained. (3) The plotted concentrations of nitrous oxide from both the arterial and coronary sinus blood should form smooth curves, indicating that there has not been irregularity of ventilation or perfusion altering the "steady state." (4) The final arteriovenous nitrous-oxide difference should not be great, since a large difference indicates that equilibrium has not been reached and hence increases the likelihood that (a) the myocardium has not been fully saturated with nitrous oxide, and therefore the final venous level may not be the same as the myocardial level; (b) some tissue other than myocardium (presumably fat) is being saturated and thus vitiating the determination, or (c) the coronary sinus specimen is contaminated by blood from a source other than the heart muscle (either anomalous venous return or right atrial blood). It is not agreed how far apart the final levels of arteriovenous nitrous oxide may be, or even that a hard and fast figure can be set, but 0.3 ml. per 100 ml. of blood has been suggested as an upper limit of acceptability. Fortunately, in most patients the final venous and arterial levels are quite close, and in those patients in whom the difference is excessive the oxygen content of the coronary sinus is frequently high enough to cast some doubt as to whether a pure specimen of myocardial venous blood was obtained. When the morphology of arteriovenous nitrous-oxide curves is unsatisfactory, or the final arteriovenous nitrous-oxide difference is excessive, or the oxygen content of the coronary sinus blood is so high as to be suggestive of contamination, it is best to discard the study as unsatisfactory.

The reproducibility of the method seems to be quite satisfactory for the individual, as indicated in studies in which repeat determinations were made in the same individuals who remained in an unchanged physiologic state throughout both studies.^{22,25} Information does not appear to be available as to whether or not the same individual studied under comparable conditions at widely separated intervals has the same coronary flow.

DISADVANTAGES AND COMPLICATIONS

There are certain disadvantages in the nitrous-oxide method of determining coronary blood flow. Not the least of these is the procedure of cardiac catheterization, during which a certain amount of apprehension on the part of the subject is natural. In addition, placement of the catheter into the coronary sinus may

be difficult because of the anatomic characteristics of the Thebesian and the Eustachian valves.¹⁴ Hellerstein and Orbison²⁷ have concluded from examination of postmortem specimens that these valves are of such disposition and character that catheterization of the coronary sinus is possible in only 75 per cent of all subjects. Clinical experience indicates that in at least 75 per cent of all patients the coronary sinus can be catheterized, depending somewhat upon the selection of cases. In very large hearts the coronary sinus, lying directly behind the large muscle mass and over the vertebral column, is in an area in which it is difficult to see fluoroscopically. The poor visibility, coupled with the irritability of the right ventricle in the region of the tricuspid valve, may be very troublesome under these circumstances. It is also a disadvantage to have to wait until several hours after the end of the procedure to know its outcome, since unexpected results must always be considered in retrospect. Another inconvenience is that it takes 10 minutes to determine coronary blood flow in addition to the time required for the determination of cardiac output, and the subject must be in a steady state throughout this period. This time factor must be considered in evaluating pharmacologic studies of agents which have a relatively short and peaked period of action.

In general, complications of the method have been those of cardiac catheterization,²⁸ consisting of supraventricular tachycardia or transient auricular fibrillation which begins during placement of the catheter, and which, on occasions, may persist after the catheter is withdrawn.^{29,30} The risk is presumed to be greater in those with heart disease or previous arrhythmias.²⁹ As with other supraventricular arrhythmias due to cardiac catheterization, response to therapy is usually prompt. Thrombophlebitis in the vein through which the catheter has been inserted is common but is usually sharply localized to the area in which the catheter entered the vein. Perforation of the coronary sinus has been reported,^{31,32} particularly in subjects in whom the catheter was thought to be in the right ventricle and was advanced in an attempt to enter the pulmonary artery. The occurrence of a pressure curve similar to that in the right ventricle on deep penetration of the coronary sinus makes this complication more likely to occur, and when it does, it may be recognized by chest pain, shock-like state, and inversion of the T waves, indicating the possibility of myocardial damage or pericarditis.^{32,33} Areas of hemorrhage into the myocardium have been reported from deep penetration of the coronary sinus in experimental animals^{33,34}; hence, deep penetration should be avoided. It seems probable that endocardial lesions and, perhaps, myocardial hemorrhages are produced more easily in the dog than in man,³⁰ by large catheters more so than by small ones, because the former completely obstruct a bigger portion of the myocardial venous outflow,³³ and by forcible penetration, particularly when it is not realized that the catheter lies in the coronary sinus instead of the outflow tract of the right ventricle and attempts are made to advance the catheter into the pulmonary artery.³⁵ Reports of damage to the coronary sinus or myocardium of man during deliberate intubation of the coronary sinus have not been found by this reviewer, but even so, caution must be observed.

NORMAL VALUES

Normal values for coronary blood flow and myocardial metabolism of oxygen and carbon dioxide as obtained by the nitrous-oxide method in several laboratories are presented in Table I. The differences shown between men and women have not been confirmed in other laboratories, but some support for the concept that such differences might exist may be derived from the following facts: (1) Testosterone is reported to have decreased oxygen consumption of tissue slices from several organs of castrated male and normal female rats.^{40,41} (2) The coronary arteries of male babies have been found to have a thicker intima and a smaller lumen than those of female babies.⁴² (3) The ratio of coronary arterial circumference to heart weight is said to be greater in the adult human female than the male.⁴³ (4) In the human being under 40 years of age there is a decidedly greater incidence of coronary artery occlusion in the male than the female.⁴⁴ (5) Smaller dogs are reported to have a higher coronary blood flow and oxygen consumption per unit weight of heart than larger dogs, apparently due to the difference in heart weight.^{45,46} Therefore, if a similar relationship exists in the human being, women, having smaller hearts, would be expected to have greater coronary flow and increased myocardial oxygen consumption per unit of heart weight. The coronary blood flow and myocardial oxygen consumption have been shown to increase in man during exercise,¹⁵ as would be expected from previous studies on experimental animals.

It has been shown that the human heart takes up various nutriment from its perfusing blood.⁴⁷ Unfortunately, data concerning these substances and their utilization have a very wide scatter,^{38,48,49} and conclusions concerning their metabolism must be in the nature of generalizations. It has been shown that the human heart takes up glucose from its perfusing blood, but that the extraction is not related linearly to the level of arterial glucose.⁴⁷ It has been concluded that the relationship between glucose extraction and arterial glucose concentration in the range between 80 and 110 mg. per 100 ml. is a function of the logarithm of the arterial glucose concentration.^{48,50} Below 80 mg. per 100 ml. the extraction of glucose was minimal, and over 110 mg. per 100 ml. the uptake appeared to be maximal and did not increase with rising levels unless the level increased rapidly.⁴⁹ With sudden increases in arterial content of glucose secondary to large infusions of glucose an upper limit of extraction seemed to be absent, and it was postulated that under these circumstances the heart stored glucose as glycogen.^{47,49} Lactate can be used by the heart muscle for the production of energy or the synthesis of glycogen, and, as with glucose, the consumption of lactate is reported to be related to the level of arterial lactate.^{47,49} Arterio-coronary sinus pyruvate differences are small, but the heart does seem to take up pyruvate from the blood stream.⁴⁹ If the carbohydrate substances taken up by the heart are completely oxidized, their aerobic metabolism is estimated to account for approximately 35 per cent of the total myocardial oxygen extraction, since the consumption of glucose accounts for 17.9 per cent, that of pyruvate for 0.5 per cent, and that of lactate for 16.5 per cent of the total.⁴⁷ It has also been established that the heart utilizes fatty acids, ordinarily accounting for 67 per cent of the oxygen usage,⁴⁷

but after a high intake of fat in some individuals the fats taken up were more than enough to account for the total oxygen consumption.⁵¹ The myocardial extraction of glucose and various amino acids is inversely related to the extraction of unesterified fatty acid.⁵² Approximately 5 per cent of the cardiac oxygen consumption may be accounted for by the uptake of amino acids, and roughly 5 per cent by ketones.⁵¹ It will be observed that the per cent of myocardial oxygen consumption attributable to each of the above, when totaled, accounts for more than 100 per cent of the oxygen consumed by the heart.⁴⁷ The error must arise from the assumption that the substances taken up are oxidized completely during the period of observation, since glucose is converted to glycogen for storage anaerobically, and fats and proteins may also be stored in the heart.

TABLE I. NORMAL VALUES IN THE HUMAN BEING

PARAMETER	BING ¹⁴ (1951)	GOODALE ²² (1953)	CALAZEL ³⁶ (1954)	KOBAYASHI ³⁷ (1956)	LEIGHT ³⁸ (1956)	ROWE ³⁹ (1959)	ROWE ³⁹ (1959)	AVERAGE OF TOTAL SERIES [#]
Number of Cases	18	5	8	15	8	15	15	84
Age (yr.)	—	—	36.54	—	36.4	26	30	30.9
Sex	—	—	6 males 2 females	—	—	Females	Males	—
Partition Coefficient	1	1.1	1	—	1.1	1	1	1(1.1)
CBF†	77	96(86)*	78	69	103(93)*	98	72	80.6(88.7)
ΔA-CSO ₂ ‡	12	—	12.2	10.5	10.3	10.9	12.3	11.4
CSO ₂ §	—	—	4.9	—	—	5.2	6.1	5.5
CMRO ₂ ¶	9.4	—	9.2	7.1	10.5(9.5)*	10.7	8.6	9.0(9.9)

*Corrected to partition coefficient of 1. for comparison with other data.

†Coronary blood flow in ml./100 Gm. of left ventricle per minute.

‡Arterial-coronary sinus blood oxygen difference in ml./100 ml. of blood.

§Coronary sinus blood oxygen content in ml./100 ml. of blood.

¶Left ventricular oxygen consumption in ml./100 Gm. of myocardium per minute.

#Numerical value of observation × Number of cases observed

Number of cases observed

INVESTIGATIONS IN DISEASE

The coronary circulation and myocardial metabolism have been studied in various disease states. In cardiac failure, coronary blood flow is slightly reduced and oxygen extraction is slightly increased but myocardial consumption per unit weight of left ventricle is normal for oxygen, glucose, lactate, pyruvates, fatty acids, amino acids, and ketones.⁵³ However, when consideration is given to the usual cardiac hypertrophy and increased heart weight associated with heart failure, there is a decreased amount of work performed per unit of oxygen consumed and, hence, a decrease in cardiac efficiency.⁵³ When cardiac muscle fiber length was calculated as related to end-diastolic volume in the right ventricle (estimated by injecting indicator into the right ventricle and sampling in the pulmonary artery), no correlation was found between myocardial fiber length and oxygen consumption in the decompensated heart.^{54,55} Whereas this constitutes suggestive evidence, it must be considered that if this method measures myocardial fiber length, it must measure those fibers in the right ventricle, whereas

the myocardial oxygen consumption is determined for the left ventricle. Although the lengths of fibers in each ventricle of the decompensated heart may be related, under some circumstances associated with failure (e.g., mitral stenosis) they almost surely are not. Subsequent to treatment with digitalis derivatives the efficiency of the recompensated heart becomes more nearly normal,^{56,57} but only minimal changes occur in the extraction of various foodstuffs.⁵⁸

In patients with arteriosclerotic heart disease and angina pectoris the coronary blood flow appears to be within normal limits, as does myocardial oxygen consumption.^{26,58,59} Coronary blood flow does not increase in response to nitroglycerin as it does in the normal subject, and hence it has been deduced that nitroglycerin relieves the pain by reducing the left ventricular work into a range that can be comfortably supported by the defective coronary vessels.^{58,59} Ligation of the internal mammary arteries for angina pectoris did not affect coronary flow significantly.²⁶ Coronary blood flow and myocardial oxygen consumption of three subjects who had had myocardial infarction was found to be reduced. This was accepted as evidence that a considerable amount of scar tissue was being perfused, and that the metabolic requirement of the scar tissue was relatively low.¹⁴

In hypertensive cardiovascular disease, coronary blood flow and oxygen consumption per 100 grams of myocardium were slightly reduced⁶⁰ or within normal limits, and coronary vascular resistance was elevated.^{5,14,55,60,61} It has been concluded from this that the myocardial weight is directly related to the amount of work required of the heart, and that the hypertensive heart undergoes sufficient hypertrophy so that the myocardial oxygen consumption per unit weight remains in the normal range.¹⁴ When hypertensive disease was due to coarctation of the aorta, however, the coronary flow and myocardial oxygen consumption were increased disproportionately while the coronary vascular resistance was normal.^{5,13,14} It would be of interest to know the comparative ages of the groups of subjects with coarctation and the normal subjects of this series, since those with coarctation tend, as a group, to come to the physician when they are relatively young. In the experimental animal, coronary flow and myocardial oxygen consumption decrease with age.⁴⁵ Similarly, in man, cardiac output decreases with age⁶² and presumably so does coronary flow.

Possibly as a result of variable restriction of blood flow in the mitral orifice, patients with mitral stenosis have been shown to have a variable decrease in coronary blood flow per unit weight.^{13,61,63} In aortic insufficiency^{5,13} with or without failure, myocardial oxygen consumption is increased,⁶⁴ but when angina pectoris coexists, there is reduced coronary flow and myocardial oxygen utilization.⁶⁴ In man with cor pulmonale, coronary blood flow had been reported to be normal⁶⁵; this should be compared with data from dogs indicating that when the pulmonary arterial pressure is elevated artificially, left coronary artery flow as measured by the rotameter increases moderately and right coronary artery flow increases considerably.⁶⁶ It is conceded, however that these are not strictly comparable situations.

In anemia there is an increase in coronary blood flow per unit of weight of heart,^{5,13,67} and when the hemoglobin is increased by transfusion of blood, the

abnormalities tend to disappear.⁶⁷ In normal men and women, coronary blood flow was correlated significantly but inversely with the hematocrit, whereas the myocardial oxygen consumption was not related.³⁹ Contrary to the first report of normal myocardial oxygen consumption in thyrotoxicosis,^{14,55} subsequent studies have revealed that human subjects with thyrotoxicosis show an increase in coronary blood flow per unit of weight of left ventricular myocardium, and an increase in cardiac oxygen consumption.^{38,68} The myocardial metabolism of glucose, lactate, and pyruvate is reported to be normal.³⁸ After successful treatment of thyrotoxicosis either by the administration of I^{131} or by thyroidectomy the abnormalities of coronary flow and myocardial oxygen consumption are corrected.⁶⁸ The heart of the diabetic subject who is not receiving insulin, as compared to the heart of a normal subject, extracts a significantly greater amount of fatty acid and ketone and a reduced amount of glucose, lactate, and pyruvate.^{69,70} Whereas one group reported results of therapy with insulin not to be as striking as might have been expected,⁶⁹ others have found that such therapy corrects the metabolism of the heart more or less completely.⁷⁰

PHARMACOLOGIC INVESTIGATION

The nitrous-oxide method is particularly well suited to the determination of the hemodynamic effects of various drugs in man. Results of such studies are especially valuable since no allowances need be made for species variation and no anesthesia is required; hence, the effect of the drug being tested alone can be determined. This is especially true if the drug acts relatively rapidly and yet has a sustained plateau of action so that the control studies can be made and followed by the experimental observations in the same subject during the same catheterization. The coronary hemodynamic effects of nitroglycerin in subjects with angina pectoris have already been discussed.⁵⁹ In subjects without angina, sublingual administration of nitroglycerin produces an increase in coronary blood flow and myocardial oxygen consumption. Indeed, myocardial oxygen consumption increased disproportionately, so that cardiac efficiency decreased. These observations raise the question whether tachycardia and myocardial metabolic alterations are more important than simple arteriolar vasodilatation in the augmented coronary flow.⁷¹ The only reservation which may be applied to this study is the relatively short and peaked period of action of this drug, and the consequent question whether the subject was in the same state for a sufficient period of time for this method to be acceptable.

Administration of strophanthus to normal men produced no change in the coronary blood flow or myocardial oxygen extraction or consumption, but since the left ventricular work decreased, efficiency was also decreased.^{14,57} As has been pointed out, the effect of digitalis derivatives is different in normal man from that found in man with cardiac failure, since efficiency decreases in the former and increases in the latter.^{56,57} Administration of acetyl strophanthidin to human subjects with a decompensated heart is associated with loss of potassium from the myocardium,⁷² similar to that occurring in experimental animals.

1-Hydrazinophthalazine (Apresoline) has been shown to increase coronary blood flow and decrease the arteriocardiac sinus oxygen difference, thus pro-

ducing an increase in the oxygen content of the coronary sinus.²⁵ This presumably means that the myocardial oxygen content is increased. Left ventricular work and cardiac efficiency were unchanged in the total series, but in isolated subjects left ventricular work was increased, and under these circumstances, if the coronary arteries are too diseased to dilate, anginal pain may ensue.

Cinnamyl Vonedrine (N methyl-N-Cinnamyl 2 phenylpropylamine hydrochloride), which is chemically related to sympathomimetic amines of the ephedrine series, has been shown to produce increases in coronary blood flow in man akin to the effects of other sympathomimetic agents in experimental animals. It produces no change in the oxygen content of the coronary sinus blood, but does produce a significant increase in coronary flow and an increase in myocardial oxygen consumption. Coronary vascular resistance decreases considerably with its administration.⁷³

Studies of the effect of aminophylline are available from two different laboratories and are of considerable interest in that, contrary to what has been demonstrated in experimental animals, both groups of investigators have found a reduction in coronary blood flow. Myocardial oxygen extraction increased, with the total amount of oxygen consumed per 100 grams of myocardium per minute remaining unchanged. Since left ventricular work decreased, there was a decrease in left ventricular efficiency.^{74,75} The reason for the discrepancy between the results in man and experimental animals is not known; however, it should be pointed out that the studies in man are done in unanesthetized individuals, and that the drug is administered intravenously, so that its effect on the body as a whole is measured rather than the effects of injection of the drug into the coronary circulation itself. Administration of atropine in man has caused an increase in coronary blood flow accompanied by an increase in oxygen extraction, increased oxygen utilization, unchanged left ventricular work, and, hence, decreased left ventricular efficiency.⁷⁶ Inhalation of cigarette smoke produced an increase in coronary blood flow, with narrowing of the arteriovenous oxygen difference so that the myocardial oxygen consumption remained unchanged. Left ventricular work decreased as did the left ventricular efficiency.⁷³

Investigation of the effects of hypoxia in the human being has shown that when subjects are exposed to 10 per cent oxygen, a considerable decrease in arterial oxygen saturation may occur, accompanied by a decrease in peripheral arterial pressure, coronary and peripheral arterial vascular resistance, and a considerable increase in cardiac output and coronary blood flow. The arterial coronary sinus oxygen difference was inversely correlated with the coronary blood flow, so that myocardial oxygen consumption remained unchanged.⁷⁷

SUMMARY

In the decade in which the nitrous-oxide method for the determination of coronary blood flow has been used, much information has been accumulated both in experimental animals and in man. The available data in man have been reviewed briefly. Since this technique is applicable to normal man in the unanesthetized state, providing he is comfortable and relatively "basal" throughout the study, information can be obtained which is reasonably accurate, free of the

artifacts produced by anesthetics, and directly applicable to man. It is clear that pharmacologic and physiologic data derived by this method circumvent the considerable difficulties which one may encounter in extrapolating from other types of studies. Furthermore, this method constitutes a valuable tool for the investigation of the effects of disease on the heart.

REFERENCES

1. Kety, S. S., and Schmidt, C. F.: The Determination of Cerebral Blood Flow in Man by the Use of Nitrous Oxide in Low Concentrations, *Am. J. Physiol.* **143**:53, 1945.
2. Eckenhoff, J. E., Hafkenschiel, J. H., Landmesser, C. M., and Harmel, M. M.: Cardiac Oxygen Metabolism and Control of the Coronary Circulation, *Am. J. Physiol.* **149**:634, 1947.
3. Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., and Banfield, W. G., Jr.: Coronary Sinus Catheterization for Studying Coronary Blood Flow and Myocardial Metabolism, *Am. J. Physiol.* **152**:340, 1948.
4. Eckenhoff, J. E., Hafkenschiel, J. H., Harmel, M. H., Goodale, W. T., Lubin, M., Bing, R. J., and Kety, S. S.: Measurement of Coronary Blood Flow by the Nitrous Oxide Method, *Am. J. Physiol.* **152**:356, 1948.
5. Bing, R. J., Hammond, M. M., Handelsman, J. C., Powers, S. R., Spencer, F. C., Eckenhoff, J. E., Goodale, W. T., Hafkenschiel, J. F., and Kety, S. S.: The Measurement of Coronary Blood Flow, Oxygen Consumption and Efficiency of the Left Ventricle in Man, *AM. HEART J.* **38**:1, 1949.
6. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure and Normal Values, *J. Clin. Invest.* **27**:476, 1948.
7. Gregg, D. E., Longino, F. H., Green, P. A., and Czerwonka, L. J.: A Comparison of Coronary Flow Determination by the Nitrous Oxide Method and by a Direct Method Using the Rotameter, *Circulation* **3**:89, 1951.
8. Conn, H. L., Jr., Anderson, W., and Arena, S.: Gas Diffusion Technique for Measurement of Renal Blood Flow With Special Reference to the Intact Anuric Subject, *J. Appl. Physiol.* **5**:368, 1953.
9. Kety, S. S., Harmel, M. H., and Broomell, H. T.: The Solubility of Nitrous Oxide in Blood and Brain, *J. Biol. Chem.* **173**:487, 1948.
10. Gregg, D. E.: *Coronary Circulation in Health and Disease*, Philadelphia, 1950, Lea & Febiger.
11. Wearn, J. T.: Morphological and Functional Alterations of the Coronary Circulation, *Bull. New York Acad. Med.* **17**:754, 1941.
12. Smith, H. L.: Relation of the Weight of the Heart to the Weight of the Body and the Weight of the Heart to Age, *AM. HEART J.* **4**:79, 1928.
13. Bing, R. J., Hammond, M., and Handelsman, J.: Coronary Blood Flow, Cardiac Oxygen Consumption and Cardiac Efficiency in Man, *Bull. Johns Hopkins Hosp.* **84**:396, 1949.
14. Bing, R. J.: The Coronary Circulation in Health and Disease as Studied by Coronary Sinus Catheterization, *Bull. New York Acad. Med.* **27**:405, 1951.
15. Lombardo, T. A., Rose, L., Taeschler, M., Tuluy, S., and Bing, R. J.: The Effect of Exercise on Coronary Blood Flow, Myocardial Oxygen Consumption and Cardiac Efficiency in Man, *Circulation* **7**:71, 1953.
16. Culbertson, J. W., Halperin, M. H., and Wilkins, R. W.: Catheterization of the Coronary Sinus in Man, *AM. HEART J.* **37**:942, 1949.
17. Soulié, P., Carlotti, J., Joly, F., and Sicot, J. R.: Catheterisme du sinus coronaire, *Arch. mal. coeur* **42**:818, 1949.
18. Gorlin, R.: Coronary Blood Flow. *In* *Methods in Medical Research*, Vol. 7, p. 121, Chicago, 1958, The Year Book Publishers, Inc.
19. Miller, G., Kaplan, B. M., and Katz, L. N.: Pressure Patterns From the Coronary Venous System in Man, *AM. HEART J.* **46**:852, 1953.
20. Harris, P., and Summerhayes, J. L. V.: Recordings of Pressure Obtained During Catheterization of the Great Cardiac Vein, *Brit. Heart J.* **17**:453, 1955.
21. Orcutt, F. S., and Waters, R. M.: A Method for the Determination of Cyclopropane, Ethylene, and Nitrous Oxide in Blood With the Van Slyke-Neill Manometric Apparatus, *J. Biol. Chem.* **117**:509, 1937.
22. Goodale, W. T., and Hackel, D. B.: Measurement of Coronary Blood Flow in Dogs and Man From Rate of Myocardial Nitrous Oxide Desaturation, *Circulation Res.* **1**:502, 1953.
23. Barger, L. M., Ehmke, D., Gonlubol, F., Castellanos, A., Siegel, A., and Bing, R. J.: Effect of Cigarette Smoking on Coronary Blood Flow and Myocardial Metabolism, *Circulation* **15**:251, 1957.
24. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique. Normal Values for Blood Flow, Oxygen Utili-

- zation, Glucose Utilization, and Peripheral Resistance With Observations on the Effects of Tilting and Anxiety, *J. Clin. Invest.* **28**:1163, 1949.
25. Rowe, G. G., Huston, J. H., Maxwell, G. M., Weinstein, A. B., Tuchman, H., and Crumpton, C. W.: The Effects of 1-Hydrazinophthalazine Upon Coronary Hemodynamics and Myocardial Oxygen Metabolism in Essential Hypertention, *J. Clin. Invest.* **34**:696, 1955.
 26. Rowe, G. G., Maxwell, G. M., Castillo, C. A., Crumpton, C. W., Botham, R. J., and Young, W. P.: Evaluation of Internal Mammary Artery Ligation for Angina Pectoris, *Fed. Proc.* **17**:521, 1959 (Abstract). *New England J. Med.* (In press.)
 27. Hellerstein, H. K., and Orbison, J. L.: Anatomic Variations in the Orifice of the Human Coronary Sinus, *Circulation* **3**:514, 1951.
 28. Simdahl, W. T.: Disorders of the Cardiovascular System Occurring With Catheterization of the Right Side of the Heart, *AM. HEART J.* **41**:204, 1951.
 29. Michel, J., Johnson, A. D., and Bridges, W. C.: Arrhythmia During Intracardiac Catheterization, *Circulation* **2**:240, 1950.
 30. Fowler, N., Westcott, R. N., and Fowler, N. O.: Disturbances in Cardiac Mechanism of Several Hours Duration Complicating Cardiac Venous Catheterization, *AM. HEART J.* **42**:652, 1951.
 31. Stern, T. N., Tacket, H. S., and Zachary, E. G.: Penetration Into the Pericardial Cavity During Cardiac Catheterization, *AM. HEART J.* **44**:448, 1952.
 32. McMichael, J., and Mounsey, J. P. D.: A Complication Following Coronary Sinus and Cardiac Catheterization in Man, *Brit. Heart J.* **13**:397, 1951.
 33. Smith, W. W., Albert R. E., and Rader, B.: Myocardial Damage Following Inadvertent Deep Cannulation of the Coronary Sinus During Right Heart Catheterization, *AM. HEART J.* **42**:661, 1951.
 34. Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., Duracher, S. H., Landing, B. H., and Banfield, W. G.: Coronary Sinus Catheterization Technique for Studying Coronary Blood Flow and Myocardial Metabolism in Vivo, *Proc. Soc. Exper. Biol. & Med.* **66**:571, 1947.
 35. Read, J. L., Bond, E. G., and Porter, R. B.: The Hazard of Unrecognized Catheterization of the Coronary Sinus, *A.M.A. Arch. Int. Med.* **96**:176, 1955.
 36. Calazel, P., Cassagneau, J., Esclavissat, M., Bollinelli, R., Dueuing, J., and Merrill, P.: Etude du debit coronaire. I, Premiere resultats chez l'homme normal. *Arch. mal. coeur* **47**:289, 1954.
 37. Kobayashi, I. G. I., Nakanishi, A., Murav, S., Shiba, M., Kato, K., Tacheuchi, Y., Yasuda, H., and Mikano Y.: Studies on Coronary Circulation in Man by the Method of Coronary Sinus Catheterization, *Jap. Circ. J.* **20**:299, 1956.
 38. Leight, L., DeFazio, V., Talmers, F. N., Regan, T. J., and Hellems, H. K.: Coronary Blood Flow, Myocardial Oxygen Consumption and Myocardial Metabolism in Normal and Hyperthyroid Human Subjects, *Circulation* **14**:90, 1956.
 39. Rowe, G. G., Castillo, C. A., Maxwell, G. M., and Crumpton, C. W.: Systemic and Coronary Hemodynamics in Normal Men and Women, *Circulation Res.* (In press.)
 40. Dennison, M. E., Jasper, R. L., Hiestand, W. A., and Zarrow, M. X.: Effects of Castration, Testosterone Propionate and Exposure to Cold on the Oxygen Uptake of Rat Tissue, *Am. J. Physiol.* **186**:471, 1956.
 41. Lacroix, E.: The Influence of Testosterone on the Respiration of Heart and Diaphragm Tissues in Female Rats, *Arch. internat. physiol. et biochem.* **64**:230, 1956.
 42. Dock, W.: The Predilection of Atherosclerosis for the Coronary Arteries, *J.A.M.A.* **131**:875, 1946.
 43. Milles, G., and Dalessandro, W.: The Relationship of the Weight of the Heart and Circumference of the Coronary Arteries to Myocardial Infarction and Myocardial Failure, *Am. J. Path.* **30**:31, 1954.
 44. White, P. D.: *Heart Disease*, Ed. 4, New York, 1951, The Macmillan Co., p. 529.
 45. Cohn, A. E., and Steele, J. M.: The Metabolism of the Isolated Heart of Dogs Related to Age, *J. Clin. Invest.* **14**:915, 1935.
 46. Spencer, F. C., Merrill, D. L., Powers, S. P., and Bing, R. J.: Coronary Blood Flow and Cardiac Oxygen Consumption in Unanesthetized Dogs, *Am. J. Physiol.* **160**:149, 1950.
 47. Bing, R. J.: The Metabolism of the Heart, *The Harvey Lectures* **50**:27, 1954.
 48. Bing, R. J.: Myocardial Metabolism, *Circulation* **12**:635, 1955.
 49. Bing, R. J., Siegel, A., Vitale, A., Balboni, F., Sparks, E., Taeschler, M., Klapper, M. and Edwards, S.: Metabolic Studies on the Human Heart In Vivo. I, Studies on Carbohydrate Metabolism of the Human Heart, *Am. J. Med.* **15**:284, 1953.
 50. Bing, R. J., and Siegel, A.: Metabolism of the Human Heart In Vivo, *Quart. J. of Phi Beta Phi*, **50**:62, 1953.
 51. Bing, R. J., Siegel, A., Ungar, I., and Gilbert M.: Metabolism of the Human Heart. II. Studies on Fat, Ketone and Amino Acid Metabolism, *Am. J. Med.* **16**:504, 1954.
 52. Gordon, R. S., Cherkes, A., and Gates H.: Unesterified Fatty Acid in Human Blood Plasma. II, The Transport Function of Unesterified Fatty Acid, *J. Clin. Invest.* **36**:810, 1957.

53. Blain, J. M., Schafer, H., Siegel, M. S., and Bing, R. J.: Studies on Myocardial Metabolism, VI, Myocardial Metabolism in Congestive Failure, *Am. J. Med.* **20**:820, 1956.
54. Bing, R. J., Falholt, W., Heimbecker, R., and Carrol, D.: Myocardial Oxidative Metabolism and Initial Fiber Length of the Failing Human Heart, *J. Clin. Invest.* **30**:630, 1951 (Abstract).
55. Bing, R. J., and Daley, R.: Behavior of the Myocardium in Health and Disease as Studied by Coronary Sinus Catheterization, *Am. J. Med.* **10**:711, 1951.
56. Blain, J. M., Eddleman, E. E., Siegel, A. L., and Bing, R. J.: Studies in Myocardial Metabolism. V, The Effects of Lanatoside-C on the Metabolism of the Human Heart, *J. Clin. Invest.* **35**:314, 1956.
57. Bing, R. J., Maraist, F. M., Damman, J. F., Draper, A., Heimbecker, R., Daley, R., Gerand, R., and Calazel, P.: Effect of Strophanthus on Coronary Blood Flow and Cardiac Oxygen Consumption of Normal and Failing Human Hearts, *Circulation* **2**:513, 1950.
58. Gorlin, R., Brachfeld, N., Bopp, P., and MacLeod, C.: Physiologic Diagnosis of Disordered Coronary Circulation, *J. Clin. Invest.* **37**:898, 1958 (Abstract).
59. Brachfeld, N., Messer, J., Turner, J., and Gorlin, R.: Physiological Evaluation of Chest Pain, *Circulation* **18**:698, 1958 (Abstract).
60. Aizawa, T., Goto, Y., Watanabe, Y., Kondo, K., Tazaki, Y., Mashima, E., Kodama, R., Yajima, O., and Takitsuka, H.: Coronary Circulation. III. Coronary Circulation Especially in Human Hypertension, *Jap. Circ. J.* **20**:301, 1956.
61. Rowe, G. G., Huston, J. H., Brown, J. F., Tuchman, H., Maxwell, G. M., Emanuel, D. A., and Crumpton, C. W.: Comparative Hemodynamic Study Including Coronary Blood Flow and Myocardial Oxygen Consumption in the Normal, Thyrotoxic, Hypertensive and Mitral Stenotic Human Subject, *Proc. Cent. Soc. Clin. Res.* **28**:65, 1955.
62. Brandfonbrener, M., Landosone, M., and Shock, N. W.: Changes in Cardiac Output With Age, *Circulation* **12**:557, 1955.
63. Read, J. L., Porter, R. R., Bond, E. G., and Bradford, S. C.: Coronary Blood Flow and Myocardial Metabolism in Valvular Heart Disease, *Circulation* **12**:762, 1955 (Abstract).
64. Christensen, R. C., Regan, T. J., Talmers, F. N., Takashi, W., and Hellem, H. K.: Coronary Blood Flow and Myocardial Metabolism in Aortic Insufficiency. Abstract of Regional Meeting, *Am. Fed. Clin. Res.*, Ann Arbor, November, 1956.
65. Rose, L. B., and Hoffman, D. L.: The Coronary Blood Flow in Pulmonary Emphysema and Cor Pulmonale, *Circulation Res.* **4**:130, 1956.
66. Gregg, D. E., Pritchard, W. N., Shipley, R. E., and Wearn, J. T.: Augmentation of Blood Flow in the Coronary Arteries, With Elevation of Right Ventricular Pressure, *Am. J. Physiol.* **139**:726, 1943.
67. Kobelt, C., Christensen, R. C., Ord, J. W., Powsner, R., Takashi, W., Regan, T. J., and Hellem, H. K.: The Coronary Circulation in the Anemic Human Subject, *Clin. Res. Proc.* **5**:292, 1957 (Abstract).
68. Rowe, G. G., Huston, J. H., Weinstein, A. B., Tuchman, H., Brown, J. F., and Crumpton, C. W.: The Hemodynamics of Thyrotoxicosis in Man, With Special Reference to Coronary Blood Flow and Myocardial Oxygen Metabolism, *J. Clin. Invest.* **35**:272, 1956.
69. Ungar, I., Gilbert, M., Siegel, A., Blain, J. M., and Bing, R. J.: Studies on Myocardial Metabolism. IV, Myocardial Metabolism in Diabetes, *Am. J. Med.* **18**:385, 1955.
70. Goodale, W. T., Olson, R. E., and Hackel, D. B.: Contrasting Patterns of Myocardial Metabolism in Diabetes, Cardiac Failure and After Insulin Administration in Man, *Clin. Res. Proc.* **1**:86, 1953 (Abstract).
71. Smith, M. H., and Gorlin, R.: Nitroglycerin: Its Effect on the Coronary Circulation and Myocardial Metabolism in Man, *Circulation* **14**:1002, 1956 (Abstract).
72. Regan, T. J., Christensen, R. C., Wada, T., Talmers, F. N., and Hellem, H. K.: Myocardial Response to Acetyl Strophanthidin in Congestive Failure: A Study of Electrolytes and Carbohydrate Substrates, *J. Clin. Invest.* **38**:306, 1959.
73. Traks, E., Hackel, D. B., and Sancetta, S. M.: General and Coronary Hemodynamic Effects of a Sympathomimetic Amine, Cinnamyl Vonedrine, *Circulation* **18**:789, 1958 (Abstract).
74. Christensen, R. C., Gray, M., Abramson, H., Kobelt, C., Baer, L. J., and Hellem, H. K.: The Effects of Aminophylline on the Coronary and Peripheral Circulation in Patients With Emphysema, *J. Clin. Invest.* **37**:884, 1958 (Abstract).
75. Maxwell, G. M., White, D. H., Jr., Crumpton, C. W., Rowe, G. G., and Castillo, C. A.: Effects of Intravenous Aminophylline Upon Coronary Hemodynamics and Myocardial O₂ and CO₂ Metabolism in Normal and Diseased Hearts, *Circulation* **18**:757, 1958 (Abstract).
76. Gorlin, R.: Studies on the Regulation of Coronary Circulation. I. Atropine-Induced Changes in Cardiac Rate, *Am. J. Med.* **25**:37, 1958.
77. Hellem, H. K., Ord, J. W., Talmers, F., and Christensen, R. C.: Effects of Hypoxia on Coronary Blood Flow and Myocardial Metabolism in Normal Human Subjects, *Circulation* **16**:893, 1957 (Abstract).

Special Article

On the Dynamics of Cardiac Muscle*

Otto Frank

Translated by Carleton B. Chapman, M.D., and Eugene Wasserman, M.D.
Dallas, Tex.

TRANSLATORS' NOTE

The name of Otto Frank, one of the great cardiovascular physiologists of all time, is well known to students of cardiovascular physiology in the English-speaking world. One gets the impression, however, that the significance of his work is imperfectly understood, possibly because none of his major works has been translated into English. Probably his greatest work, *Zur Dynamik des Herzmuskels*, is difficult to follow in its entirety even in English, but in its original German it is much too formidable to be approached at all except by accomplished linguists. The following translation, work on which began nearly a decade ago, is offered in the hope that it will bring Frank and English-speaking students into something more than superficial contact.

Frank's style is verbose, repetitive, and often obscure. The enormous technical detail in the paper is, to say the least, tedious, and it is difficult to resist the temptation to omit some of it. It was felt, however, that the danger of omitting useful information was much too great, especially when one begins to appreciate the fact that the author was considerably ahead of his time in his exquisite appreciation of the necessity for applying sound physical principles to the study of biological systems. Specific examples are his keen awareness of the need for adequate response characteristics in systems for recording pressure, and his meticulous development of valid equations of cardiac work. His advances in

From the Cardiopulmonary Division, Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex.

Expenses in connection with the translation were met by funds from the Dallas Heart Association and the U.S. Public Health Service (Grant No. H-2113 [C3]).

Received for publication March 18, 1959.

*Frank, O.: *Zur Dynamik des Herzmuskels*. *Zeitschrift für Biologie* 32:370-447, 1895.

both these areas seem to have been neglected by many cardiovascular physiologists, and it is doubtful that the care taken by Frank, especially in recording variations in pressure, is matched by more than a very few contemporary investigators.

But the most significant contribution in the paper is the principle which was later studied and extended by Starling and co-workers. After reading Frank's paper, one must acknowledge the justice in Wezler's recent remark: "The so-called *Law of the Heart*, which Starling rediscovered ten years later [than Frank] for the warm-blooded heart and which is linked with Starling's name especially in the English literature, is implicit in Frank's work on cardiac dynamics. One should, more properly, speak of the *Frank-Starling Law of Cardiac Work*, as suggested by Gremels."¹ Frank's observations constitute the transitional link between work on skeletal muscle by Blix and von Kries and that on cardiac muscle. At the very outset of his paper, he equates change in length of skeletal muscle with change in ventricular volume, and change in tension with change in intraventricular pressure. Then, using an isometric contraction method, he shows clearly that "The peak of the isometric curves rises with initial tension (filling). . . . Beyond a certain level of filling, the peaks decline. . . ." The same relationship is also shown to prevail in the atrium. Still later, acknowledging the previous contributions made by Dreser and Blasius, he indicates that the same relationship exists between initial ventricular tension and ejected volume. His final statement on the point is: ". . . a simple *a priori* relation between length and tension does not exist in cardiac muscle for every moment of its action but . . . the mechanical conditions under which the muscle has functioned before this instant have a decisive influence." He leaves little doubt that end-diastolic filling, and hence volume, is the significant item, although his actual measurements did not include volume as such. It remained for Starling and others to follow the changes in ventricular volume and to specify initial fiber length as the prime determinant of work done during the following contraction. The validity of the Starling extension (and the significance of the basic Frank-Starling relation in the intact animal) are still in question at the present time. Although modern technical advances offer promise that the basic concept can at last receive adequate testing, our understanding of the concept and its implications is not very different from Frank's own.

Other major contributions include important observations on atrioventricular valvular insufficiency, retrograde flow with closure of the aortic valve, and the logical division of the cardiac cycle into phases on the basis of dynamic events within the heart. Innumerable ideas and suggestions are encountered, many of which are currently being investigated. Indeed, the most striking feature of the paper is its astonishing currency. It is a labor to read, but it is the source of so much that is now accepted, and provides so many fresh viewpoints, that the serious student is more than adequately compensated for his trouble.

In rendering the translation, some license was thought to be necessary for the sake of clarity. Some words, however, are invariably translated literally. Where Frank uses *Spannung*, the translation is always *tension*; where he uses

Druck, the translation is *pressure*. At some points, Frank appears to use the two words interchangeably. At other points, he uses *Spannung* (tension) to refer to tension in the ventricular wall according to the Laplace formulation. Similarly, the word *Geschwindigkeit* (velocity) is used at times to refer to velocity of flow, and at other times, to linear velocity. It is also used to indicate velocity of shortening of myocardial fibers (*Verkürzungsgeschwindigkeit*).

The relationship between flow, pressure, and velocity as discussed by Frank is difficult to fathom unless one carefully follows the argument from the beginning. In deriving velocity curves from pressure curves, he is dealing primarily with data obtained from an artificial circulatory system containing rigid tubes. The relationship between pressure and linear velocity in systems embodying elastic tubes, as Frank points out toward the end of the paper, is considerably more complex. Nevertheless, the final work equation given in the paper is valid for the intact (natural) circulatory apparatus, provided pressure and velocity curves are separately recorded. In a later paper,² Frank takes this into account when he elaborates the work equation in a more refined form.

Frank was born on June 21, 1865, in Gross-Umstadt in Odenwald, and died in Munich on November 12, 1944, "in the Fatherland's darkest hour . . . as the dreadful bomb-filled nights of the German cities announced the fall of the West. . . ."¹ He studied medicine at Kiel and Munich, and, realizing that a standard medical education was not adequate for a career in basic physiological research, he invested two more years in the study of mathematics, physics, chemistry, and zoology at Heidelberg, Glasgow, Strassburg, and Munich. He began his research career with Carl Ludwig at Leipzig, but moved to Voit's laboratory in Munich in 1894. After spending the period 1905 to 1908, as professor of physiology at Giessen, he returned to Munich as Voit's successor. Here he remained until 1934, when, partly owing to political considerations, he was forced to accept emeritus status.

His bibliography, as assembled by Wezler,¹ consists of 131 items and discloses that his initial interest was in fat absorption. With the publication of *Zur Dynamik des Herzmuskels* a long series of papers on circulatory physiology and instrumentation was inaugurated. The series includes some of the most basic papers on recording techniques ever written, as well as the classic *Die Grundform des arteriellen Pulses*.² Virtually every physical phenomenon relating to the movement of blood in the natural circulatory system came under his scrutiny during his long career, and the full extent of his contribution can hardly be determined unless and until the entire output of this ingenious and indefatigable man is carefully collected, studied, and critically reviewed. It is easily discernible, however, that Frank belongs alongside the greatest in the field, and that a reasonable starting point for any new cardiovascular investigation is his bibliography.

REFERENCES

1. Wezler, K.: Otto Frank zum Gedächtnis, *Zeitschrift für Biologie* 103:90-122, 1950.
2. Frank, O.: Die Grundform des arteriellen Pulses, *Zeitschrift für Biologie* 37:483-526, 1899.

Although the mechanical activity of skeletal muscle has been widely studied under the most varied conditions, very little has been done along these lines with cardiac muscle. Examination and analysis of mechanical relations in the heart of warm-blooded animals, while the organ is still inside the body, are subject to great difficulties. The motion is so rapid that recording devices are taxed to the utmost. The main difficulties for analysis lie in the very complicated mechanical conditions under which [cardiac] motion takes place, and in that one cannot arrange [experimental] conditions arbitrarily without endangering the life of the animal.

Only with the study of the isolated heart is it possible to set up mechanical conditions under which cardiac motion takes place at will. For the special purpose of permitting protracted observation, we have at our disposal the cold-blooded heart, and, in particular, the frog heart.

A method for the solution of the mechanical problems relating to cardiac motion is available; it follows the same pattern which Fick and von Kries used in their studies of skeletal muscle and may be set out as follows.

The heart should first be observed under the simplest mechanical conditions. As such, one may first study the *isometric curve*, in which the length of muscle elements remains unaltered while tension is caused to vary. Then one should study the *isotonic curve*, in which changes in length are recorded while tension remains unaltered. Finally, the investigator should introduce, one by one, the several variables which condition the various phenomena as they occur in the intact animal. Such variables include interruption of [fluid] motion by closure of valves, altering motion by use of variable resistances, and the interposition of elastic factors.

Length and tension changes in skeletal muscle correspond to changes in volume and pressure [in the heart]. By measuring these values and establishing their time relationships, one is able to examine the play of forces in the entire heart.

In some of the methods used for the graphic investigation of motion of the isolated cold-blooded heart, as, for example, in that of Gaskell¹ or in the suspension method of Engelmann,² only a few of the components of cardiac motion or cardiac forces are measured and their direction cannot always be established.

The method employed mainly by the school of Ludwig, in which the heart is connected to a mercury manometer, cannot be used for the solution of the problems mentioned, since in this arrangement the lengths and tensions change simultaneously in a particular manner which has not yet been investigated [even] in skeletal muscle. Neither do the methods of Marey,³ Blasius,⁴ Williams,⁵ Dreser,⁶ and Hürthle⁷ suffice for these purposes, either because the heart is left from the outset within the complicated conditions of the intact circulation, without being subject to more minute scrutiny, or because the methods record no more than a single instant of cardiac motion occurring under simple conditions. The very important motion of the atrium is not considered at all by most of these methods.

I was, therefore, forced to develop my own method for the solution of the mechanical problems of cardiac motion. I present here a diagram of the com-

plete apparatus as it is constituted at present (Fig. 1). Various parts of it may be omitted, depending on one's actual needs.

From the blood-reservoir the perfusing blood (usually bovine or sheep's blood diluted 1:4 with physiologic salt solution) flows through Valve I to the cannula, which leads into the atrium through the inferior vena cava, all the other veins being ligated. The blood then makes its way into the ventricle and into Aortic Cannula II, which has been inserted through the aortic valve into the ventricular cavity; from this point blood moves to Valve II, and thence, through a tube of variable length, it empties into special measuring vessels or is led back to the blood-reservoir.

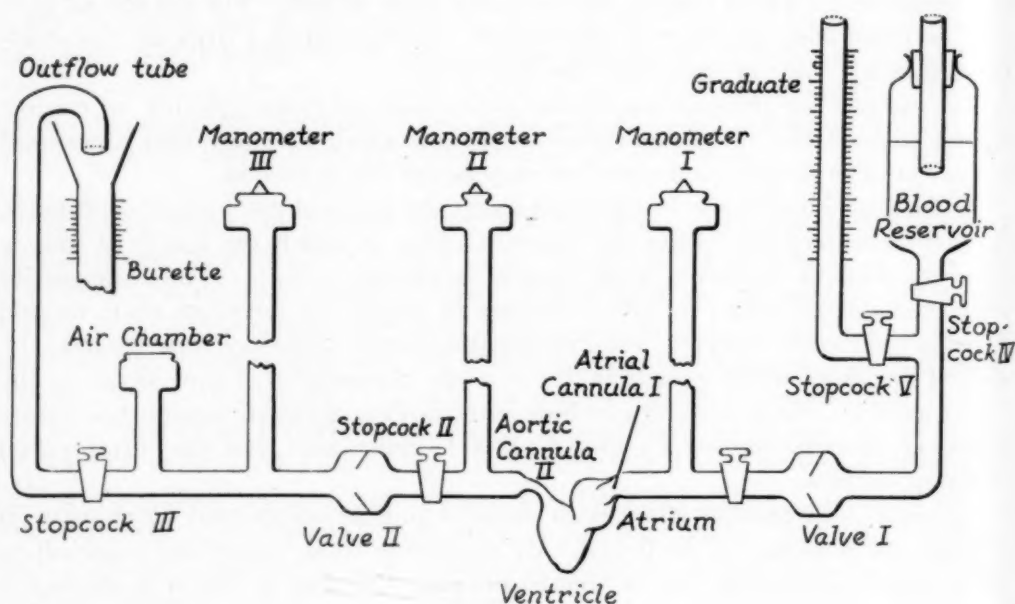


Fig. 1.

The blood-reservoir can be elevated on a stand and the level held constant by insertion of a glass tube like that in a Mariotte bottle. In some cases the heart is perfused from a graduated cylinder, which allows rapid readings to 0.01 c.c., instead of from the larger reservoir. Separation of the two sources is accomplished by Stopcocks IV and V.

Distal to Valve I is Stopcock I,* for shutting off perfusing fluid, and proximal to Valve II is Stopcock II, for shutting off the ventricle. Stopcock III serves as resistance control, and an air chamber can be inserted proximal to it to serve as an elastic factor.

Measurement of the ejected blood is done either by putting a burette under the outflow tube or, for measuring smaller quantities, by actually weighing the ejected volumes. As a rule, the volume ejected in many pulsations, 10 or 20 altogether, is measured. By means of a type of flowmeter arrangement the number of pulsations, of which the total volume is to be measured, can be marked on a kymographic drum.

*Not labelled in Fig. 1. It lies between Valve I and the atrial cannula.

Lateral pressures between Stopcock I and atrium, between Ventricular Cannula II and Stopcock II, and distal to Valve II, are measured with Manometers I, II, and III, respectively. The tubes which lead to the manometers are filled with physiologic salt solution. The principle of fluid transmission introduced by Hürthle had to be applied in our case so that the fluid displacement, which of necessity takes place into the manometers, was minimal. In this way, flow in the circulating system is influenced as little as possible by movement of fluid in the manometers. Characteristic oscillations were, in general, less disturbing on account of the relatively slow changes in motion. For these reasons I made the diameter of the rubber membranes in the manometers as small as possible. For Manometers I and III, I used capsules with membranes of 7-mm. diameter, and for Manometer II, membranes of 4-mm. diameter. The movements of the membranes were transmitted to light writing levers by fine ivory pins glued to the membrane.

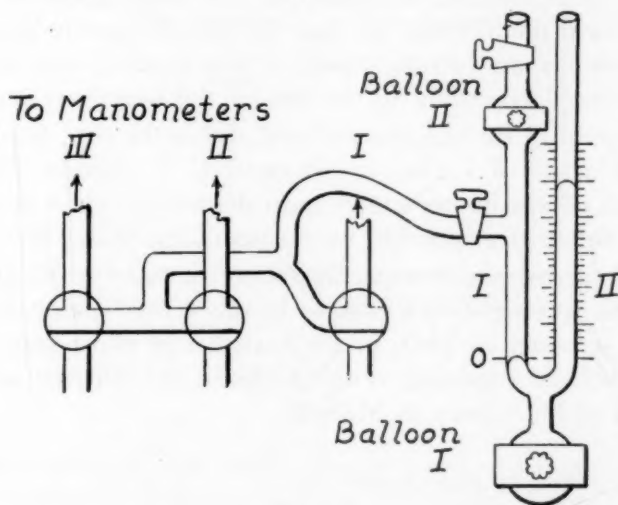


Fig. 2.

In order to calibrate the manometers I do not connect them directly to the tube system, but connect them by means of three-way stopcocks to a mercury manometer, as shown in Fig. 2. By appropriate setting of the stopcocks, the mercury manometer can be connected with each of the three rubber manometers (as in Fig. 2), or the three rubber manometers can be directly connected with the tube system of the circulation by switching off the mercury manometer. It is also easy to see that, by changing the stopcock setting, pressure in any one of three places can be measured with any of the manometers (e.g., the pressure proximal to Stopcock II with the more sensitive Manometers I and III), without disturbing the regular connection of the tubes.

The tube connecting with the mercury manometer is likewise filled with salt solution, as is the left limb of the mercury manometer down to the mercury meniscus. In order to introduce pressures for comparison, mercury is forced from rubber balloon I through a set screw into the manometer. It naturally

rises highest in limb II, [in which] it is elevated to the level desired. But it also rises slightly in limb I, since a small quantity of fluid enters the rubber manometer system. In order to maintain the level in limb I constant, I affixed to it a second rubber balloon, II; by compressing it, zero level can be restored. The apparatus thus embodies a mercury manometer with a constant zero point. At the beginning of each experiment the zero point is brought to the level of the opening of the atrial cannula, so that all pressure readings in the various manometers refer to this zero level. I shall not go into detail about calibration, which can be carried out quickly and easily with this arrangement. By rapid squeezing of balloon I, numerous [calibration] lines are quickly produced.

All the glass tubes of the system are 4 mm. in internal diameter and are connected by thick rubber tubes. The atrial cannulas measure up to 2.5 mm. in internal diameter; the arterial cannula is made of metal and has an internal diameter of 1.0 and 1.5 mm., according to the size of the heart. The valves are patterned after those used by Williams, but the inner tubes are fabricated from perfectly cylindrical metal tubes so that the membranes fit better. The entire apparatus is made fast to a strong stand. - I take especial care that the cannulas, which can be altered according to the size of the heart, are installed properly.

The movements of the manometer level and of the time marker are recorded on the smoked drum of Ludwig's kymograph. I transfer the very delicate and symmetrical curves immediately⁸ onto diapositive chlor-brom-silver plates. They are then enlarged accurately by means of the Abbe drawing instrument.

All in all, I carried out 59 experiments on the heart of *Rana esculenta*. The main part of the investigation was done in the winter semester of 1892-93, and in the summer semester of 1893, in the Institute of Physiology at Leipzig, but I did some additional experiments as checks in the summer semester of 1894, at the Institute of Physiology in Munich.

THE ISOMETRIC CURVES OF THE VENTRICLE

I record the changes in intraventricular tension, volume remaining constant, in the following manner: The ventricle is completely closed off by shutting Stopcock II; it remains in communication with Manometer II, which comes off the aortic cannula, but cannot empty its contents. Then, by turning off Stopcock I, Manometer I simultaneously records the isometric curve of the atrium. Movement of fluid into the manometers is prevented as much as possible by making the membranes of the manometers very small (that of Manometer II is only 4 mm. in diameter). In order to show the average maximum of the isometric curve (about 6 cm. Hg), only 2 mm.³ need enter, a very small volume in proportion to the content of the ventricle. Thus, the pure isometric state is probably achieved as well with this method as with those used for skeletal muscle.

Quite early, I made observations which caused me to change the procedure somewhat. I noted that when Stopcock II was turned suddenly, disturbances in cardiac activity in the form of tetanic, or runs of, contractions almost always occurred. Furthermore, I noted that the peaks and form of the curves written by the manometer were not equal, but varied according to the filling of the heart.

Thus, I was induced to study first of all the influence of filling, or, what amounts to the same thing, the influence of the initial tension on the form of the curves. With filling, initial tension changes according to the laws of the distensibility curve of the resting heart muscle. I therefore applied the following method: By closing Stopcock I, I prevented the flow of blood to the heart, which was then allowed to eject its contents. This was achieved, except for a small, constant residual, by a few contractions. Only then did I close Stopcock II. From this point on, the manometer registered the isometric curve at very low filling. Next, I admitted a small amount of blood (about 0.1 c.c.) from the graduated cylinder which was closed off from the reservoir. Atrial contraction then forced this blood into the ventricle and I obtained an isometric curve at higher filling, and so on. To make this procedure clearer, the apparatus used is again shown in Fig. 3.

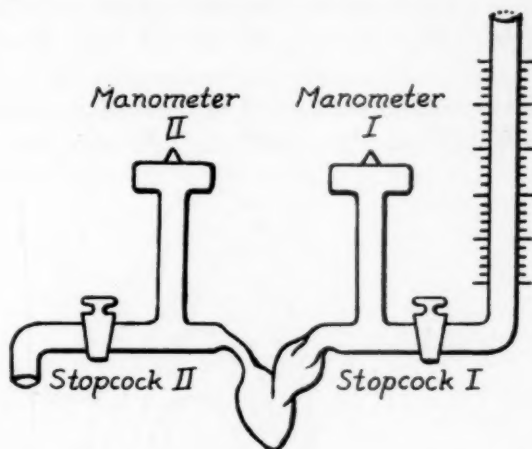


Fig. 3.

With gradual filling of the heart, runs of rapid contractions occurred very seldom. I discovered the following law concerning the dependence of the form of the isometric curve on the initial tension: The peaks (maxima) of the isometric curve rise with increasing initial tension (filling). (I call this part of the family of curves the first part.) Beyond a certain level of filling, the peaks decline (second part of the family of curves). The curves broaden steadily with increasing filling, and the area enclosed by the tension curve and the abscissa (the integral of tension) increases steadily, and does so even in the second part. Fick⁹ discovered the same law for skeletal muscle. These relations are represented graphically by the curves in Figs. 4 and 5, taken from Experiments 48b and 51b.

In general, the initial parts of the curves are convex relative to the abscissa; then, from a transitional point they become concave and remain so up to the peak and down to a second transitional point, when they again become convex. The transitional point on the ascending limb shows especially well in curves of the first part of the family of curves. The ascending limb becomes steeper and steeper with increasing tension. In the second part of the family of curves the steepness decreases somewhat. With higher initial tension, the change of tension in the atrium becomes visible in the beginning of the ventricular curve.

In order to demonstrate the dependence of the tension peaks on the degree of heart filling, I selected the following experiments from the large number of studies I have carried out. Filling is assumed to be represented by the amount of blood allowed to enter the heart. It is also assumed that the content of the heart is initially zero, which is not quite the case.

Experiment 27:

Volume (c.c.)	0	0.18	0.34	0.47	0.63	0.84	0.93
Tension peak (mm. Hg)	12	60	68	66	60	59	58

Experiment 27b:

Volume (c.c.)	0	0.09	0.22	0.36	0.48	0.68	0.95
Tension peak (mm. Hg)	12	48	66	70	67	64	58

Experiment 32:

Volume (c.c.)	0	0.18	0.40	0.51	0.70	0.87
Tension peak (mm. Hg)	12	35	57	54	48	45

Experiment 44:

Volume (c.c.)	0	0.12	0.20	0.33	0.43	0.56
Tension peak (mm. Hg)	10	44	58	57	54	43

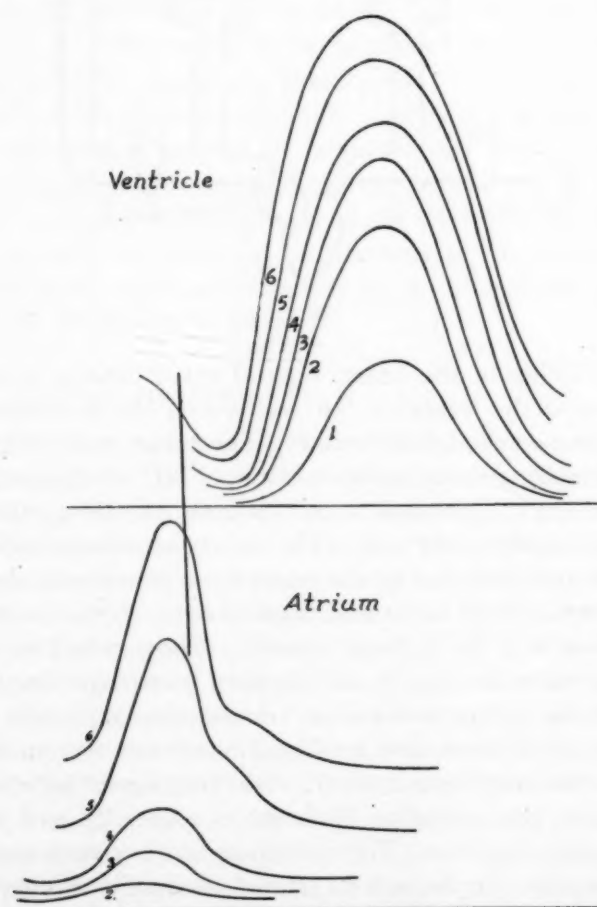


Fig. 4.—Experiment 51b. Family of isometric curves during increasing filling: Part 1.

Experiment 55:

Volume (c.c.)	0	0.10	0.20	0.31	0.45	0.55
Tension peak (mm. Hg)	20	51	68	63	61	56

Fick derived a stretch (distensibility) curve for active skeletal muscle from such groups of curves; in actual fact, he arranged the peak values (maxima) of the individual curves as functions of the fiber lengths, which, of course, remain virtually unchanged during isometric contraction.⁹ I could proceed similarly with respect to the heart if I could regard maximal tensions as functions of cardiac filling. This is made difficult by the fact that in my method ventricular filling is not precisely measured. Although the atrium transmits increasing volumes of blood to the ventricle as we increase the flow into the atrium itself, it does not empty entirely. It thus comes to contain more and more blood, as is seen clearly in Figs. 4 and 5. The conditions for establishing a distensibility curve would be present if the ventricle were tied off completely and artificial stimulation applied as needed. This is to be undertaken at a later date. Concerning the theoretical assumptions which are fundamental for such considerations, I shall say a few words further on, and will also examine critically the distensibility curve as determined by Dreser.⁶

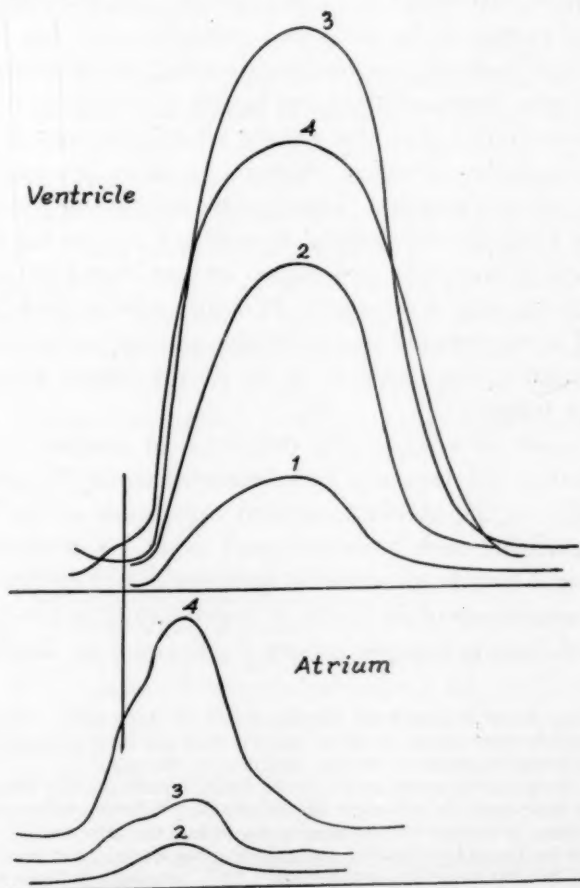


Fig. 5.—Experiment 48b. Family of isometric curves. Curves 1 to 3 fall in Part 1; Curve 4 is in Part 2.

Among the maximal values of the isometric family of curves is one which has attained particular significance in physiology: it bears the label *absolute strength*.^{*} Edward Weber equated absolute strength with the weight which, when hung onto the muscle at the moment of stimulation, prevented its shortening without causing elongation. With the experimental tools available to him, Weber was not able to determine this value, or could do so only very inexactly. It later became possible, by means of Helmholtz' after-load method,[†] to measure absolute strength in the dissected frog muscle. In this procedure, the muscle is supported with a certain initial tension, so that it does not lift the *after-load* until it has reached a tension equal to its weight. The largest after-load, which it is then able barely to lift, is the absolute strength, provided that the initial tension is equal to, or close to, zero. We see that in this case the mechanical conditions are the same as those under which the muscle labors in isometric contraction. We also see that the maximal tension of isometric contraction occurring with the natural length of the resting muscle (the length of the unstretched muscle) is equal to the absolute strength. The natural length of [cardiac] muscle cannot be made out easily in our experiments. No conclusions can be drawn from the initial tension because the levels of the curves at the beginning of the contraction [end-diastolic], which correspond to initial tension, are too low in Part 1 of the isometric family of curves to be measured precisely.

However, it can be shown approximately which of the curves in the family corresponds to the one obtained when the length of muscle is natural. Schwann and Hermann¹⁰ have found that the weight which the muscle is able to lift in the after-load contraction becomes smaller the more we support the muscle (starting from the natural length). This finding falls under the above-mentioned law established by Fick for the skeletal muscle and by me for the heart muscle: the maximal tension of isometric contraction at first increases with augmentation of the initial length (or initial tension). It is inherent in the above law that the absolute strength[‡] is represented by one of the maximal tensions of the first part of the isometric family of curves; it is, as Fick's curves show,⁹ probably the largest in absolute terms.

In order to reach an unequivocal definition of absolute strength, I should like to propose that in the future it be considered equal, for skeletal [as well as for cardiac] muscle, to the absolute tension maximum of the isometric family of curves (calculated for each cross-sectional unit). Certain difficulties in determining the natural length are common to skeletal and cardiac muscle.

The absolute maximum of an isometric curve family in a series of experiments involving repeated determinations occurs [each time] in response to the same

^{*}[The term *absolute Kraft* is translated *absolute power* by Tigerstedt. As defined in this paper, however, *absolute strength* is more nearly accurate, since it does not refer to power or force in a physical sense. It is defined in terms of pressure (see last footnote on this page).]

[†][In this method, the muscle is attached to a lever which is mechanically supported so that weights hung on the lever (the after-load) do not affect the muscle until it begins to contract. The weights are not lifted until the tension developed by the muscle overcomes the after-load.]

[‡]Absolute strength [or force] is expressed per unit of cross section, and maximal tension (equal to a hydrostatic pressure) has the same dimensions— $\text{ml}^{-1} \cdot \text{t}^{-2}$. [Pressure is force/area, and force = mass (m) \times acceleration (a). Acceleration is lt^{-2} , so that the term *ma* becomes $\text{ml} \cdot \text{t}^{-2}$; pressure thus becomes $\text{ml}^{-1} \cdot \text{t}^{-2}$.]

degree of filling. If one allows the same amount of blood, that previously was found to correspond to absolute strength, to flow slowly into the heart, one is sure to obtain the same absolute maximum again, provided no unusual events have intervened between tries.

PROOF:

Experiment 27: absolute maximum at 0.34 c.c. filling

Experiment 27b: absolute maximum at 0.36 c.c. filling

Dreser (and earlier, Williams) used his own method to measure the absolute strength of the heart muscle. He noted the height to which the isolated frog heart was able to drive blood into a vertical tube. He then considered the hydrostatic pressure of this column of blood to represent absolute strength. According to the preceding argument this height is not identical, as such, with absolute strength.* In Dreser's own experiments it is not identical, but is much smaller. Dreser, in fact, uses an initial tension in his determination that is equal to the optimal load, about which I shall have more to say later. According to his statement, the optimal load amounts to 20 to 30 cm. of blood, or 1.6 to 2.3 mm. Hg; in my experiments the absolute maximum of the isometric curve family, which approaches the absolute strength, was reached with an initial tension of about 1 to 4 mm. Hg. After this absolute maximum the maxima (peaks) of the isometric curves begin to decrease, so that in Experiment 44, for example, they fell from 58 mm. Hg (absolute maximum of tension), with an initial tension of 1.6 mm. Hg, to 43 mm. Hg (tension), with an initial tension of 3.2 mm. Hg, a value which lies far below Dreser's optimal load. Hence, the values which he obtained as absolute strength are considerably less than mine: he observed them to fluctuate between 35 and 75 cm. of blood, while mine lay between 70 and 108 cm. in various heart preparations. The heart must be markedly overdilated by these extraordinarily high initial tensions, a fact which is stressed by various investigators who have used Dreser's method.¹¹ Objection is voiced especially because of changes in ejection following the determination of absolute strength. When the procedure as I have described it is meticulously applied, such disturbances rarely arise.

PROOFS:

Experiment 17:

12:00—absolute strength = 62 mm. Hg

6:00—absolute strength = 61 mm. Hg

(24 isometric pulses)

pulse volume just before = 0.335 c.c.

pulse volume just afterward = 0.337 c.c.

Experiment 26:

12:36—pulse volume = 0.381 c.c.

1:00—absolute strength = 61 mm. Hg

(about 80 isometric pulses)

pulse volume immediately afterward = 0.377 c.c.

*Dreser makes a similar observation in his own paper.

Experiment 27:

- 4:50—absolute strength = 64 mm. Hg
- 5:58—pulse volume = 0.230 c.c.
 - absolute strength = 63 mm. Hg
 - (about 80 isometric pulses)
- 6:15—pulse volume = 0.226 c.c.

Experiment 32:

- 4:23—absolute strength = 57 mm. Hg
- 4:37—pulse volume = 0.313 c.c.
 - absolute strength = 53 mm. Hg
- 5:00—pulse volume = 0.282 c.c.
- 5:08—pulse volume = 0.210 c.c.
 - (different initial tension)
 - absolute strength = 52 mm. Hg
- 5:15—pulse volume = 0.22 c.c.

Experiment 47:

- 12:20—absolute strength = 57 mm. Hg
 - (about 120 isometric pulses)
- 1:10—pulse volume = 0.168 c.c.
- 1:21—absolute strength = 52 mm. Hg
- 3:25—pulse volume = 0.140 c.c.

Experiment 48:

- 1:00—absolute strength = 59 mm. Hg
- 1:22—pulse volume = 0.277 c.c.
 - absolute strength = 59 mm. Hg.
- 2:37—pulse volume = 0.251 c.c.

Experiment 51:

- 11:50—pulse volume = 0.269 c.c.
- 11:57—absolute strength = 58 mm. Hg
 - (about 100 isometric beats)
 - pulse volume immediately thereafter = 0.268 c.c.

Experiment 52:

- 6:10—absolute strength = 55 mm. Hg
- 6:45—absolute strength = 55 mm. Hg
 - pulse volume before = 0.154 c.c.
 - pulse volume immediately after = 0.165 c.c.

It goes without saying that, for comparisons of this sort, the frequency of the heart beat is constant. This is easy to follow in my technique, since the frequency is constantly recorded.

It is also noteworthy that Dreser's determination of absolute strength is, of course, dependent on the ability of both valves to close, and that still other phenomena may have contributed to the inexactness of his determination. Specifically, there seems to be a drawback in many experiments which is difficult to avoid, and which may lead to considerable distortion of isometric curves (Figs. 6 and 8): the atrioventricular valve, which is essential in all methods, very frequently becomes insufficient.* It is easy to prove that curves like those in Figs. 6 and 8 actually are produced by insufficiency of the atrioventricular valve.

*Previously observed by Blasius.⁴

In the first place, direct observation establishes it, since, in such cases, blood is always seen to move retrograde during ventricular contraction. But the insufficiency also finds graphic expression in the atrial curve (Figs. 6, 7, and 8). Finally, the curve of the completely isolated (tied-off) ventricle does not show a bend [such as that seen on the descending limb of the ventricular curve in Fig. 6]. One may close off any portion of the ventricle, however small, but the shape of the isometric curve as described above is invariably maintained (Experiment 33). One can often avoid insufficiency by appropriate placement of the cannulas, which in my apparatus may be changed with ease and certainty.

The appearance of insufficiency is, however, to some extent predictable, which fact in most cases permits an evaluation of the curves. For one thing, one notes the remarkable phenomenon that, in spite of existing insufficiency, the maximum of the isometric curve is reached in the great majority of the cases since the valves are not insufficient at the beginning of the contraction. Proof for this is found in the following: In the first place, the relation of the peaks of the curves is exactly the same in contractions occurring in the presence of insufficiency as was previously described [when insufficiency was absent]. (The examples mentioned in Experiments 27 and 32 are cases of this nature.) It may also happen that the curve registered in insufficiency shows a higher maximum, if the valve again becomes sufficient as filling increases, than that of the heart with normal valve function; insufficiency could be expected to have the opposite effect (see Figs. 6, 7, and 8). In the second place, the increase in pressure in the atrium indicative of valvular insufficiency occurs in these experiments well after the beginning ventricular contraction and does not begin before the ventricular curve has reached its maximum. Figs. 6 and 8 provide examples of this relationship.

I believe this remarkable phenomenon must mean that at the beginning of the contraction the muscle ring to which the atrioventricular valve is fastened is able to offset the [rising] tension, but that it later becomes dilated, permitting the valve to become functionally insufficient. It is of interest that a similar observation may also be made in connection with human valvular disease. Professor F. Moritz has informed me that in some valvular defects of the atrioventricular valves a distinct interval between the first heart sound and the cardiac murmur occurs. This would be analogous to the phenomenon noted by us and might well be explained in the same way.

Another characteristic of insufficiency is the fact that frequently insufficiency is present when filling is small but disappears when filling becomes larger (Figs. 6, 7, and 8). The reason for this may be similar to that just given: at lower fillings, the ventricular wall, and the valvular ring, are folded together during diastole. This change in the position of the insertion of the valve interferes with its operation. With an increase in filling, the heart gradually assumes a definite shape, namely, that of a sphere, the valvular ring becomes circular, and the valve becomes sufficient. In some cases the valves remain sufficient until just at the end of isometric contraction, when a backflow of blood into the atrium takes place. This phenomenon may be a manifestation of a principle that stems from an investigation by von Kries¹²: under certain conditions, the muscle in every

phase of its activity is able to exert less than normal force. The experimental method used by von Kries could be applied, perhaps, to cardiac muscle, and the validity of his conclusions tested with regard to it.

Thus, we succeed in the great majority of cases in determining at least the ascending part of the isometric curve, and particularly in measuring the absolute strength. It would appear at first glance that a method which, like Dreser's, involves the ventricle alone is preferable to our own because it avoids troublesome valvular insufficiency. In fact, this has been pointed out as an advantage of Dreser's method.¹³ This, however, is an illusion. In Dreser's procedure the atrium cannot actually be removed, but must be left attached in order to provide the ventricle with its natural stimuli, on which its regular rhythm depends.

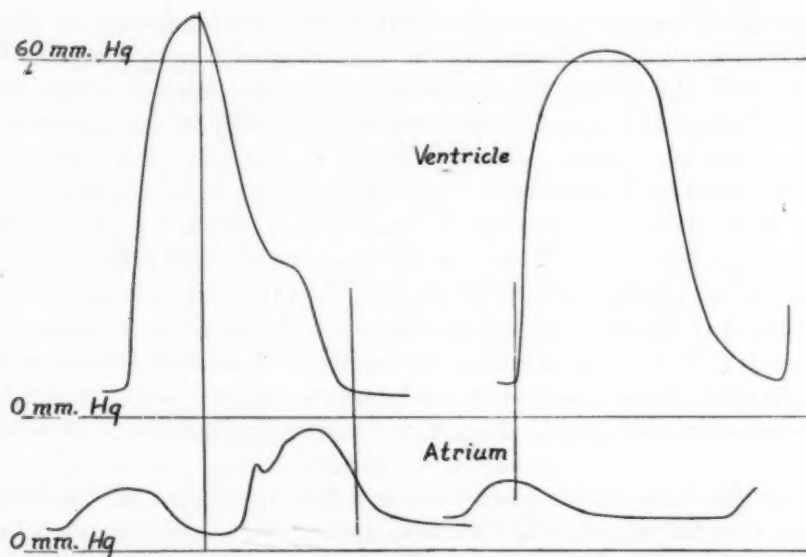


Fig. 6.

Fig. 7.

Fig. 6.—Experiment 42. Isometric curves of atrium and ventricle during insufficiency of the atrio-ventricular valve.

Fig. 7.—Experiment 42. Isometric curves after the valve has become competent.

There is still the possibility that the unpredictable influence of insufficiency will be present, just as in my own arrangement. Dreser experienced this difficulty himself when he carried out his determination of the distensibility curve. We may well require that, in determinations of the absolute strength, insufficiency of the valve be taken into account. My method permits one to evaluate this factor more exactly and to determine by observation of atrial contraction the degree of the effect attributable to insufficiency. Another advantage of the method is that determination of the absolute strength is achieved in a few beats,* while in Dreser's arrangement the heart has to work a considerable time against abnormally high resistances. Still more significant is the fact that with the new

*Hürthle's method has the same advantage.⁷ The above remarks apply in other respects to his method.

method one can follow, in most cases at least, the entire course of the energy curve, and not merely changes in the ordinate, however remarkable. It is clear from the beginning that the entire course of the curve is important and meaningful for the calculation of cardiac work under exact conditions.

I should like to say a few more words about runs [of contractions] and about tonus-like contractions which occur with sudden increase of pressure in the ventricle. They have also been observed with sudden constriction of the aorta in the warm-blooded heart.¹⁴ Such contractions are prolonged in a tetanic manner; tension does not fall to the normal level [between them], and single beats have the appearance of small excursions superimposed on a very prolonged contraction. (See Fig. 9.)

Occasionally, the peak of the curve exceeds the absolute strength slightly. But when the isometric procedure is used with gradual [in lieu of sudden] filling, the number of contractions is not usually changed in spite of the significant increase in pressure during ventricular activity. Very noteworthy is the fact that I was unable to observe any change in pulse rate attributable to rise in pressure either in the venous or in the arterial system. I intend to return to this problem at the proper time.

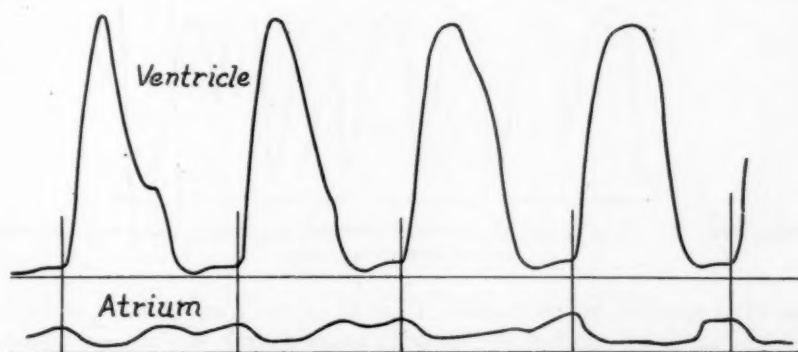


Fig. 8.—Experiment 54. Isometric curves of atrium and ventricle. Atrioventricular valve is incompetent at first, but as the filling pressure rises, the valve becomes competent (sequence runs from left to right).

In the course of an experiment, runs of beats sometimes occur without evident reason. They are especially likely to appear if the experiment lasts a long time, and they manifest themselves in innumerable ways. Two forms of runs appear to me especially interesting. Specifically, one sees not only that runs of an equal number of beats repeat themselves one after the other (forming, for example, repeated runs of five beats each), but that the beats in such runs are different as to timing and form; moreover, the same internal differences are clearly seen in groups of runs following each other. Thus, it is the form of one heart beat that determines the form of the next one, and so on, so that completely repetitive forms of the individual runs occur (Experiments 26c and 34b). (See Fig. 10.)

Especially frequent are runs of two beats each. (One recalls that such [double beats] are also observed in warm-blooded animals and are responsible for many forms of bigeminy.) A forceful beat and a weak beat follow each other

alternately. If, as happens frequently, this double beat changes gradually to a regular rhythm, the weaker pulse usually undergoes the most important changes, but the stronger one also changes by becoming somewhat smaller. It would seem that the main contraction is also abnormal! These characteristics remind one very much of the phenomena associated with Marey's refractory period. A study of these items might be of some interest for the theory of the initiation of contraction.

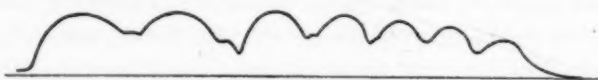


Fig. 9.—Experiment 18. Runs of contractions associated with sudden increase in filling pressure.

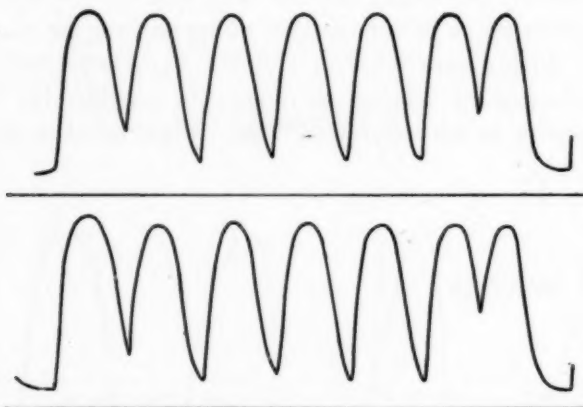


Fig. 10.—Experiment 32. Two runs of contractions of seven beats each, the lower run having immediately followed the upper.

In spite of specific investigation, I could never find an indication in the isometric curves of a suction effect, as it is observed in the warm-blooded heart. If, as is frequently stated, the negative pressure in the ventricular curves of the warm-blooded heart is due to elastic forces, themselves due to change in ventricular shape, one would not expect it in this sort of study; there is no change in ventricular shape with isometric contraction.

THE ISOMETRIC CURVE OF THE ATRIUM

In my method, changes of tension in the atrium are registered simultaneously with those in the ventricle. However, such changes do not take place under purely isometric conditions, since blood ordinarily flows out of the atrium into the relaxed ventricle during diastole, and the atrium, especially when initial tension is low, contracts slightly. But it can be recognized, nevertheless, that in most cases the ventricular curve starts shortly after the atrial curve has reached its maximum. In the presence of high initial tensions the increase in pressure attributable to atrial contraction becomes manifest in the ventricle. (See Fig. 11.)

The isometric curve of the atrium can be determined more precisely if we study the atrium alone. If we place a ligature at the atrioventricular border,

the ventricle stops while the atrium continues to beat undisturbed. This modification of the method is extremely convenient and provides the possibility of studying the isolated atrium continuously for an hour, provided the blood contained in it is renewed from time to time.

The isometric curves of the atrium show the same peculiarities as those of the ventricle, the same changes with changing initial tension.

In order to ascertain the relation between the absolute strength of ventricle and atrium, one must first determine the absolute strength of the ventricle; the atrium is then immediately tied off and its absolute strength determined.

	ABSOLUTE STRENGTH OF		
	VENTRICLE	ATRIUM	RATIO A/V
<i>Experiment 47:</i>	45 mm. Hg	7 mm. Hg	0.15
<i>Experiment 48:</i>	48 mm. Hg	6 mm. Hg	0.15
<i>Experiment 49:</i>	57 mm. Hg	8 mm. Hg	0.13
<i>Experiment 53:</i>	47 mm. Hg	10 mm. Hg	0.21

The ratio thus fluctuated between one eighth and one fifth of the absolute strength of the ventricle. It is probably desirable to repeat the experiments using fresh hearts, since the above studies were done with very fatigued ones.

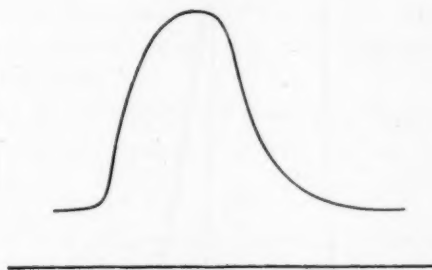


Fig. 11.—Experiment 49. Isometric curve of the atrium.

THE ISOTONIC CURVE OF THE VENTRICLE

I have not yet obtained direct records of isotonic ventricular contraction curves. Nevertheless, I can incompletely characterize them from the results of some of my experiments. Before I go on with this, I shall briefly indicate the methods by which one can obtain approximately isotonic curves of the heart.

We consider a contraction of the skeletal muscle to be isotonic if the length of the muscle, but not its tension, undergoes a change.⁹ It is measured in skeletal muscle by having the muscle pull at a lever which is fitted with a weight. Incidentally, if the weight is attached along the axis and the force of inertia is diminished as much as possible, jerking is prevented.

The problem for heart muscle consists in following changes in volume in such a way that no concomitant changes in tension take place.

In clarifying my assumptions as far as is necessary at this point, it is to be understood that tension, which is to remain constant, is equated with the hydrostatic pressure that bears upon the inner surface of the heart (dimension

$m \cdot l^{-1} \cdot t^{-2}$). One can easily convince oneself that if, during the contraction of a hollow muscular organ, hydrostatic pressure is unchanged, the tension acting on each cross-sectional unit must decrease. But it should be considered that in *isotonic* contraction of skeletal muscle, as generally defined, the tension on the cross-sectional unit does not remain constant, but, in fact, decreases. Since this decrease is probably of the same magnitude as that of a hollow muscular organ, the isotonic state of the heart as defined above may justifiably be taken as analogous to that of skeletal muscle. In addition, most statements concern comparisons of the course of contraction in which the predominant change is in *length*, with that in which the main change is in *tension*; for such comparisons, as will be shown below, contractions need be only approximately ideally isometric or ideally isotonic. With regard to the degree of approximation which suffices, I shall have more to say when I have actually applied the methods which I now wish to describe.



Fig. 12.—Experiment 26b. *a*, Time of isometric maximum. *b*, Closure of aortic valve (arterial curve)

In order to realize the isotonic state in the above sense, one must cause the heart to work against a resistance that is held as constant as possible, and record changes in volume. This is achieved, in contrast to the isometric method, by having the heart work against a very inelastic rubber manometer, such as a Marey capsule. Or, one may register photographically the oscillations of the meniscus moved by the column of blood as it is lifted by the heart. Or, one may measure changes in volume with a piston recorder. Which of these three methods is to be preferred is unknown, since a suitable evaluation of them has not yet been provided.

In all these procedures, unavoidable changes in tension (changes of hydrodynamic pressure owing to friction, etc.) can be measured easily by attaching a low-volume manometer near the heart laterally to the tube which connects the heart with the registering apparatus. An elastic manometer with a very small membrane surface is suitable. This arrangement corresponds to that which Blix¹⁵ introduced into muscle physiology in order to measure changes in tension and length during contraction of skeletal muscle; by its use it has been shown that even with the utmost decrease of the moment of inertia, no contraction of the skeletal muscle is purely isotonic in the sense that there are no concomitant changes in tension relative to the unit of muscle cross section.

I can now draw some conclusions from my experiments with regard to the form of isotonic contraction curve. From further discussion it will become clear that one may envisage the contraction of the heart, as it takes place in my circulatory model, as an after-load contraction in which shortening occurs approximately isotonicly. It is clear, then, that maximal contraction must coincide with cessation of blood flow out of the heart into the aorta; in general, it is synchronous with closure of the aortic valve. The moment of closure of the valve is thus the same as the time of maximal shortening. As we shall see further on, use of the after-load method serves to place maximal shortening earlier than the maximum of the isotonic curve, but it nevertheless always falls later than the maximum of the isometric curve (see Fig. 12). Fick¹⁶ found (in this connection) that for skeletal muscle the maximum of the isotonic curve occurs later than that of the isometric one.

The following table gives the times from the beginning of ventricular activity to the maximum of the isometric curve and to the aortic valve closure. (Time of heartbeat = 1.)

EXPERIMENT NUMBER	TIME TO MAXIMUM OF ISOMETRIC STATE (SEC.)	TIME TO VALVE CLOSURE (SEC.)	DIFFERENCE (SEC.)
12b	0.38	0.46	0.08
12c	0.40	0.53	0.13
17	0.36	0.49	0.13
17c	0.36	0.45	0.09
25b	0.31	0.57	0.26
26b	0.31	0.50	0.19
29b	0.35	0.57	0.22
32b	0.31	0.53	0.22
Mean	0.35	0.51	0.16

From Fig. 12 (and the table) we can therefore conclude with certainty that in cardiac muscle, as well as in skeletal, the maximum of the isotonic curve occurs later than that of the isometric curve, even though the single curves were not recorded precisely enough to permit exact measurement.

Experiments with the artificial circulation also provide quantitative information about another feature of the isotonic curve: the level of maximal

shortening. It is equal to the value of the ejected volume. Furthermore, the value of maximal shortening, like that of skeletal muscle, decreases with increasing load. Of this more will be said when the distensibility curve is taken up.

In addition, one may make a few suppositions concerning the isotonic curve, since curves expressing velocity of shortening (the curve of the first derivative of the isotonic curve) can be approximated. From such curves, one can reconstruct the volume curve.

I intend to establish all these facts quite clearly with one of the methods already described. It is highly likely that the comparative study of isotonic and isometric curves will give us important information for the understanding of the action of toxic agents and of nerve stimuli. According to previous investigations it is very improbable that the changes in isotonic and isometric curves due to toxic effects run parallel. I call to mind in this connection the fact that digitalis causes an increase in ejected volume, while the absolute strength remains unchanged (Williams, Dreser).

ARTIFICIAL CIRCULATION WITH RIGID TUBES

The mechanical conditions, which we have treated in the preceding investigation in their simplest form, become very much complicated when we put the heart in an artificial circulation made up of a part of the heart (atrium and ventricle) and of rigid tubes. Fig. 1 shows the circulation as I arranged it, except that the air capsule and Stopcock III were omitted. It should be noted that all tubes were the same size (4 mm. in internal diameter); this made it possible to bring the ends of the rigid tubes into close approximation so that the elasticity of the rubber connecting tubes could have no influence [on the response characteristics of the system]. In order to follow changes in tension during contraction, manometers were placed in the system at the following points (attached laterally, as in Fig. 1): Manometer I in the tubing before its entry into the atrium; Manometer II between the ventricle and Valve II; Manometer III in the tubing distal to Valve II. The arrangement permitted measurement of pressures in atrium, ventricle, and the artificial arterial system. The ventricular manometer, which was exposed to large variations in pressure, was fitted with a very small membrane surface (4 mm. in diameter).

In cardiac contraction occurring under such conditions, both length (volume) and tension change. In addition, events are further complicated by the fact that valvular action divides the cardiac cycle into several periods; these, in turn, differ among each other by the different sorts of relationships between change in tension and change in length that occur during them. For clarification of what follows, three pressure curves (arterial, ventricular, and atrial) are presented (see Fig. 13).

THE PRESSURE CURVE IN THE VENTRICLE

As a result of the opening and closing of the aortic valve, the pressure curve of the ventricle is divided into three sections. The first section extends from the closing of the atrioventricular valve to the opening of the aortic valve. During

this time no movement of blood takes place; the pressure in the ventricle has first to reach the level required to overcome the tension in the arterial system. This period is called the strain phase of ventricular contraction [isometric contraction]. The second section lasts from the opening to the closing of the aortic valve. During this period the blood is driven from the ventricle into the aorta. This is the ejection phase of ventricular contraction. Then, after closure of the aortic valve the ventricle relaxes again: we call this part of the cardiac cycle the relaxation period. It is subdivided into two sections, as we shall soon see.

Concerning the first phase, or strain phase, the law of isometric contraction is followed perfectly; no change in volume occurs during this time. The duration of this phase is related to the pressure prevailing in the arterial system; the higher the pressure the longer its duration. The steepness of the increase in pressure is determined by the degree of the ventricular filling. With increase in ventricular filling, steepness increases to a certain degree and then decreases according to the principles established for the isometric curve.

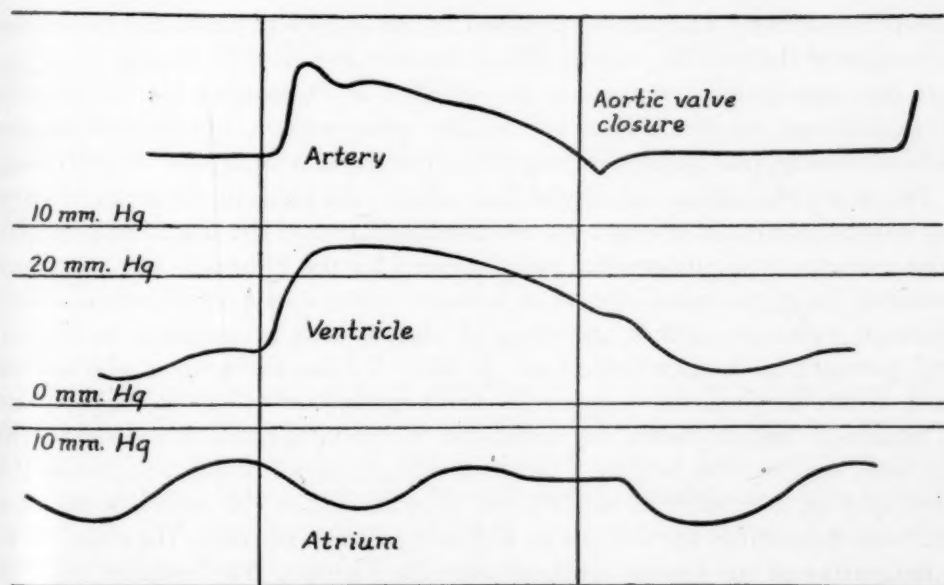


Fig. 13.—Experiment 17b. Pressure curves from atrium, ventricle, and artery (without Valve I.)

The analysis of the second section, the ejection phase, is considerably more difficult. If no frictional resistance occurred during the movement of fluid, this part of the curve would run purely isotonically* in our arrangement. The resistance opposing the cardiac contraction would always remain the same, and would be equal to the hydrostatic pressure of the column of fluid which rests upon the heart in the arterial system. Thus, [during ejection] we would not obtain an arterial pressure but a straight line running parallel to the abscissa.

But this is not the case. The resistances in the arterial tube and particularly in the artificial aortic valve cause pressure to change during this phase in a definite

*[The use of *isometrisch* at this point in the original is obviously in error.]

manner. It is clear that frictional resistance is a function of the speed of flow. If Poiseuille's law, proved by Jacobson¹⁷ for wide tubes, is valid for conditions in which there are rapid changes in velocity of flow, the resistances would be proportional to the velocity of the blood. Poiseuille's law states: velocity v is directly proportional to coefficient R (which depends on the nature of the fluid), to the square of the radius of the tube r^2 , to the lateral pressure H , and inversely to the tube length l ; therefore,

$$v = \frac{R}{\pi} \cdot r^2 \cdot \frac{H}{l}$$

Thus, in the case in which the length of the tubes was left unchanged, the lateral pressure was proportional to the velocity of flow, since the cross section of the tubes remained constant (2 mm.²).

Therefore, we have to assume that this portion of the pressure curve is the same as the curve of velocity of flow. Its time relationships are identical with those of the curve of change in volume. The velocity curve is the first derivative of the volume curve. The surface enclosed by the [velocity] curve and its abscissa (the integral of the velocity curve) should measure the ejected volume.

If the assumptions concerning the validity of Poiseuille's law be granted, then, in this case, we would have the peculiar phenomenon, not yet investigated in skeletal muscle, that tension is proportional to the first derivative of shortening.

The minor changes of velocity of flow which take place in the artificial circulation hardly justify, in themselves, the assumption that the law is inapplicable. On the contrary, one can marshal definite proof for the Poiseuille law. It would be possible, using the same system of tubes, to carry out hydrodynamic studies at different velocities of flow and thus, at various sites in question, to measure lateral pressure for known velocities. If then, for the ordinate of the ejection portion of the pressure curve, one puts down the known values for velocity and thus obtains a velocity curve, the integral of the curve is equal to ejected volume if the basic assumption is right. Further definite proof of the applicability of the law may be inferred from the fact that if (with one of the methods described above) one determines the volume as well as the pressure curve, the curve of the first derivative of the former [volume] must be identical [run parallel] with the pressure curve. I have not established precise proof [for the above], but I can show that the integral of the pressure curve of this period [ejection] increases with the ejected volume and that it is approximately proportionate to it.

How does one define the part of the curve that corresponds to ejection? The arterial curve provides the necessary means. As soon as movement of blood takes place, lateral pressure in Manometer III must undergo change according to the principles just discussed; it must, in fact, rise above the pressure which the resting column of fluid exerts on the heart. (It should be remembered that on account of the particular means of calibration used, hydrostatic pressures are reckoned by using the level of the heart as the zero reference point.) This rise above the pressure of the resting column of fluid occurs when blood flows out of the heart; the pressure falls below it when blood flows back into the heart. The ejection period thus begins at the instant the pressure curve begins to rise above

the [base] pressure line which runs parallel to the abscissa and represents the pressure of the overlying [resting] column of fluid. In other words, it begins at the moment the (artificial) aortic valves open, and terminates at the instant the pressure curve reaches the base line (begins to descend below it) (Fig. 13).

Measurement of the areas of these portions of the curves in the same heart shows that the areas are approximately proportional to the ejected volumes (Figs. 18 and 19). The proportionality of ejected volumes and the area of the arterial curves are shown in the data below. It is clear that the relation *area/volume* remains approximately constant during an experiment; hence, proportionality prevails between area-integral and volume. From this it follows with great probability that the Poiseuille law applies in this situation and that the velocity curve is inherent in this portion of the pressure curve. Even though the pressure ordinates may not be exactly proportional to the velocities, the form of the pressure curve must correspond in general to the velocity curve. The peaks ultimately attained usually coincide.

	AREA (mm. ²)	EJECTED VOLUME (c.c.)	AREA VOLUME
<i>Experiment 17c:</i>			
	21.2	0.22	96
	27.5	0.27	101
	37.5	0.34	109
<i>Experiment 26:</i>			
	7.5	0.07	107
	12.0	0.11	114
	24.0	0.22	109
	61.5	0.52	118

Arterial pressure curves thus point also to changes in volume, and we find combined in them the same features that Blix and Schoenlein obtained for skeletal muscle by simultaneous registration of activity using a length-tension recorder.

The maximal [flow] velocity I have observed (Experiment 26) was 0.75 c.c. per second, with a stroke volume of 0.524 c.c., and the average [linear] velocity of a fluid moiety was 59 mm. per second.

The pressure curve of the ejection period shows several characteristic features. The curve rises rather rapidly and soon reaches a maximum, which also represents maximal velocity. According to known rules of mathematical analysis, this velocity maximum corresponds to a turning point of the shortening curve or, in other words, to the point at which the second derivative of the curve becomes zero. It follows that at that point the part of the [ventricular] shortening curve, which previously had been convex with reference to the abscissa, now becomes concave. Acceleration, which was previously positive, then becomes negative.

At this same point one almost always finds a sharp spike, especially pronounced in the arterial curve. Is this spike caused by actual movement of the blood or is it to be ascribed to [the response characteristics of the] manometer? The fact that the spike is almost completely missing in the ventricular curve

indicates that the latter is the case. It would have to be present [in the ventricular curve] also if it were produced by an oscillation in the column of fluid, since in the ejection portion of the curve the contents of the ventricle and artery have free communication.

That the spike does not appear in the ventricular pressure curve, or if so only slightly, may well be due to the use of a manometer with a smaller membrane surface. The latter is not as likely to show artefactual oscillation as the arterial manometer.

Such artefacts at this particular point are most likely produced by the magnitude of negative acceleration of the whole system (column of fluid, membrane, and recording apparatus) during the rather sudden transition from the steep rise at the maximum [to the descent]. This is why we do not see artefacts in isometric curves, traced by the same manometer, which have a rise just as steep and which reach still higher pressure values: the course of the isometric curve changes much more gradually. The fact that this artefact always occurs in the same location seems remarkable to me. As I shall discuss in more detail, this phenomenon should be taken into consideration in accounting for oscillations (anacrotic waves) in the ascending portion of the pulse curve. If one wishes to reconstruct the true course of such a distorted curve, one must follow the example of Helmholtz¹⁸ and connect the points at the beginning and end of the artefact; they then become points on the correct curve.

After the maximum the curve descends more or less rapidly. I should like to voice at this point my opposition to the expression *plateau*, sometimes used to designate this part of the pressure curve. It may lead to misunderstanding. A plateau, in the sense that the pressure curve runs parallel to the abscissa longer than an infinitely short time, does not exist. It cannot exist, considering the continuous course of pressure and velocity curves. The impression of a sudden turn of the curve into a horizontal part may be produced in part by the artefacts already mentioned, and in part by inaccuracies in recording. To be sure, pressure changes much more rapidly at the site of the artefact than in an isometric contraction or in a muscle contraction generally, as we have just seen. That this change in pressure occurs with various speeds under various conditions may be the reason for the fact that certain investigators have sometimes found a *plateau*, sometimes none. These differences can be easily understood from my curves. If *plateau* is taken to designate the apex of the ventricular curve (ejection pressure curve) without conveying an impression concerning the course of the curve, an expression is introduced which is not ordinarily used in the mathematical analysis of curves.

At the end of the arterial curve, where pressure again reaches the hydrostatic pressure of the [resting] arterial column of fluid, there is a bend of the curve below the horizontal pressure line. This cannot be due to manometric artefact, as a glance at those arterial curves in which elevation is small will show. It can also be seen, in most of the curves, that this dip is steeper than the preceding fall in pressure. The opposite would occur in an artefactual oscillation. Therefore, this fluctuation in pressure must indicate retrograde flow. The question arises as to whether this retrograde movement of the blood is a peculiarity of

our apparatus (possibly the consequence of faulty closing of the artificial valves), or whether it occurs with each valvular closure—even that of natural aortic valves. The latter condition seems to me to be the case.

The aortic valve begins to move toward its closed position near the end of the expulsion period as velocity of flow begins to fall off. This movement is assisted by eddy formation, as Ceradini has observed. At the moment of closure the valve is still oriented in the direction of flow, particularly if velocity at the end of ejection has remained high. At the instant at which dilatation of the ventricle begins, the valve descends toward the ventricle. The descent reflects movement of the overlying column of blood, which movement then causes the valve to close. In addition, we are dealing with an elastic, expansile membranous structure. We assume therefore that closure of such a valve involves retrograde flow of blood. A valve which would sink down again by its own weight would behave differently.* The faster the change in the direction of flow takes place, the more forceful the retrograde movement. There may well be [at the instant of closing] a small amount of regurgitation. The retrograde movement of fluid may take place in cardiac contraction with greater or lesser velocity, as will be shown later.

The instant at which the pressure curve begins to fall below the pressure base line is very likely coincident with the maximum of the curve of shortening. Under certain conditions it may correspond to the time of the peak of the isotonic curve, provided the changes in pressure during ejection are not too great.

After the aortic valves close, the third period of ventricular activity begins. We call it the relaxation period. The arterial curve of our rigid-tube circulatory apparatus runs horizontally from this point onward, except for a few small vibrations immediately after closure of the valve. Whether the latter are caused by characteristics of the manometer or by oscillations of the entire column of fluid on the valve membrane in its resting [equilibrium] position, I shall leave undecided for the moment. The horizontal course of the pressure curve indicates good closure of the artificial valve. The course of ventricular contraction again becomes purely isometric after valve closure. This lasts but a very short time and terminates when blood flows from atrium to ventricle.

Pressure in the ventricle falls rather rapidly during the relaxation period, for two reasons. First, the ventricular volume is more or less diminished because of ejection, and the part of the curve which follows immediately upon valve closure corresponds to an isometric contraction occurring with lower initial tension than that prevailing during the contraction of the initial [isometric] phase. Second, as we have explained, aortic valve closure, coinciding with the maximum of the isometric curve, falls later than the maximum of the isotonic curve, and is on the descending part of the isometric curve. Nevertheless, tension does not become zero immediately after valve closure but remains [significantly above zero] for varying lengths of time, depending on prevailing conditions.

The notch in the descending part of the ventricular pressure curve which coincides in time with aortic valve closure originates in the following manner:

*This view is similar to Fick's.¹⁹

the retrograde flow of blood at the closure of the aortic valves causes a lowering of the hydraulic pressure, and only after the retrograde flow of blood has stopped does hydrostatic pressure become recorded as lateral pressure. If we assume that closure of the valve occurs instantaneously without retrograde flow, the pressure curve would take the form of that represented by the dashed line in Fig. 14.

When the pressure of the blood in the atrium has reached the pressure prevailing in the ventricle, flow from atrium to ventricle begins. Atrium and ventricle form a single cavity, and the curve sector concurrent with this period is common to both cavities. One should, however, consider this portion of the cardiac cycle in the discussion of the atrial curve.

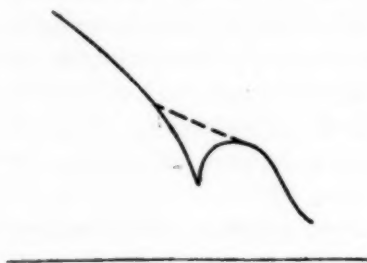


Fig. 14.—Diagram of the course of pressure in the ventricle near the time of valve closure. Compare with Fig. 19.

THE PRESSURE CURVE OF THE ATRIUM

In analyzing the atrial curve, we must keep separate the two procedures which I have used to move blood into the atrium. To prevent retrograde flow during the atrial contraction, in one series of experiments I inserted a valve in front of the atrial cannula [between atrium and cannula]. In another series of experiments I allowed the blood to enter directly into the atrium through a wide tube. If inflow and outflow of blood into the ventricle take place through the same cannula, as in the Williams-Dreser method, two valves must naturally be used. Analysis of the first technique provides the simplest presentation of atrial pressure events (Fig. 15).

To get some idea of pressure magnitudes, one should recall that movement of fluid toward the heart lessens the lateral pressure, and that the opposite movement increases it; this is according to known laws of hydraulics as already applied in the case of the ventricular pressure curve. The amount of increase or decrease in pressure depends on the velocities, and with methods which employ a valve it is not to be disregarded, since the valve imposes considerable resistance.

I begin the discussion of the atrial curve at the instant at which ventricular filling begins. The blood in the atrium has reached a certain pressure, sufficient to overcome pressure in the ventricle and to drive blood into it. This instant is signalled by a sharp lowering of pressure in the atrium, according to the analysis just presented. In fact, there is invariably a sharp break in the atrial curve immediately after aortic valve closure (after *b* in Fig. 15). It indicates the instant at which blood begins to flow into the ventricle.

The lowering of pressure is represented at this point by a bend which is convex toward the abscissa, and which represents a gradual slowing [of the fall in pressure]. One can arrive at a concept concerning this event in the pressure curve in the following way: Let us suppose that the entrance into the ventricle is occluded. The hydrostatic pressure thus acts entirely on the manometer. Then the entrance is suddenly opened. Pressure now sinks immediately to the very low level of the hydraulic pressure. If we now reduce the size of the inlet and thus increase resistance at this point, lateral pressure again rises by a small amount, etc.

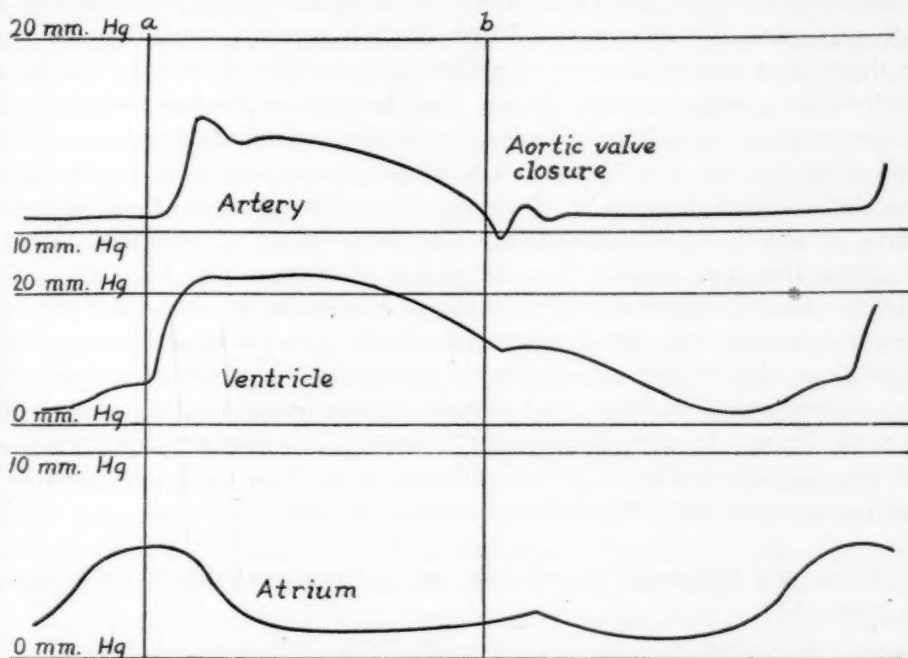


Fig. 15.—Experiment 15. Pressure curve of atrium, ventricle, and artery (with Valve I).

The pressure shown by the manometer depends therefore on the resistance prevailing at the atrioventricular opening (conditions otherwise remaining the same). The course of tension at this point will also be reflected in the manometric pressure curve. We know already that the tension curve of the ventricle forms a curvature at this point which is convex toward the abscissa. It will, therefore, be the same with the atrial curve. The fall in pressure at the end of this short episode becomes less as the ventricle fills.

The curve soon begins to rise again, forming a concavity toward the abscissa, and the atrium begins to contract, its maximal contraction occurring just before the onset of ventricular contraction. The entire course of change in [atrial] pressure, as described to this point, finds a parallel in the ventricular pressure curve. With higher atrial tensions the atrial contraction is invariably reflected in the ventricular curve.

Closure of the atrioventricular valves takes place after maximal atrial contraction (at *a* in Fig. 15). Since blood flows to the heart in larger quantities

during relaxation of the atrium, the pressure curve falls again. It then gradually rises to the point at which the analysis of the curve was begun (opening of the atrioventricular valve). The last rise can attain the level of hydrostatic pressure only if it is allowed the necessary time.

Thus we see that the atrial curve has two relative peaks: one at the instant of the opening of the atrioventricular valves, and one at the height of atrial contraction just before the closure of the atrioventricular valves. Depending on whether the filling pressure is high or low, the latter or the former becomes the absolute maximum [the more prominent] (Fig. 17, *a* and *b*). The valve actually functions only at lower filling pressures. With higher filling pressures it imposes a high resistance, and accentuates fluctuations in pressure more than is the case when the system contains no valve. With such systems, fluctuations in pressure generally take a rather similar course. But because of the low resistance [since there is no valvular resistance], tensions attain the hydrostatic level more quickly. In this situation, one usually finds a horizontal curve segment running parallel to the abscissa and showing an elevation above the abscissa which, in terms of pressure, is equal to the hydrostatic. The curve of atrial contraction rises but little above this line, mainly because of low resistance (see Figs. 13 and 18).

In the hearts of warm- and cold-blooded animals, in situ, the form of the curve varies between the two extremes described. For the most part it resembles the first type, since a not inconsiderable resistance is occasioned by contraction of the venous openings, and since venous pressure rises continuously as blood flows to the heart. In general, the atrial [pressure] curve runs more or less parallel to the velocity curve of blood [in the atrium], except that the lowest point on the [atrial] pressure curve corresponds to the peak velocity.

CHANGES OF THE PRESSURE CURVE AND OF EJECTED VOLUMES WITH CHANGE OF LOAD (FILLING)

The amount of blood ejected by the heart changes if the level of the blood-reservoir is lowered or raised, as shown by Blasius, Marey, and Dreser. Before I discuss these changes, I wish to make some explanatory remarks.

Ventricular contraction behaves in the artificial circulation approximately like an after-load contraction: at the beginning [of the cycle], tension is lower than during contraction; the valve, which protects the resting ventricle from tensions in the arterial system, in a sense replaces the support screw used in the after-load method for skeletal muscle. A change in the level of the blood-reservoir alters the tension prevailing at the beginning of contraction (initial tension). Or, expressed in another manner, one changes the *Ausgangshöhen*.^{*12} It is clear, in fact, that with the change of initial tension the initial length of the resting muscle, or, in this case, the volume at the beginning of the contraction, is also changed. For this reason, if one [lowers the reservoir until it corresponds to a volume that is less than initial], the volume of fluid may not fill the cavity of the resting heart completely; the walls of the chamber may then come incompletely

^{*}[This word literally means *initial elevations* or *intensities*. English physiological usage appears to provide no exact counterpart.]

into contact. In the case of skeletal muscle this would correspond to a situation in which its initial length has not yet reached the length of the resting unloaded muscle. The raising of the blood-reservoir is comparable to the lowering of the support screw in the skeletal muscle preparation, and vice versa.

It is very seldom correct to assume that initial tension is equal to the hydrostatic pressure exerted by the column of fluid between the level in the reservoir and that in the heart. As has been made clear, this tension does not always equal that in the atrium because the flow of fluid past resistances proximal to the heart, and especially past the resistance offered by the valves, can lower lateral pressure considerably. Also, the time available for flow is frequently not sufficient to allow filling of the atrium to the tension of the hydrostatic pressure. We therefore always determine initial tension by measuring directly the atrial or ventricular pressure at the beginning of ventricular contraction.

If one raises the inflow level higher and higher above the heart, as Dreser* (and still earlier, Blasius) showed, the ejected volumes increase to a certain limit (the *optimal load*), and then decrease again. This determination, to my mind, may not be very precise, owing to the method of measurement. For, as we have seen, the prevailing pressure in the ventricle—the initial tension—is below the hydrostatic pressure. The level of fluid in Experiment 26 was, for example, 20 cm. above the heart, and the actual initial tension in the ventricle amounted to no more than 13 cm. Dreser's *optima* are thus too high. If, during an experiment, the same initial tension is maintained, the correction of pressure measurements may be of little importance, since the experiments are mostly concerned with relative determinations on the effects of toxin or nerve stimulation. But this is not necessarily the case, even when the level of the fluid above the heart remains unchanged. When the cardiac rate slows, the initial tension prevailing in the heart approaches the hydrostatic. It may be that consequent alteration of ejected volume is attributable to the action of toxins, but, in all probability, it is due to change in initial tension. That such a rise in initial tension actually occurs with slowing of the pulse rate can be shown by consideration of pressure curves obtained during vagal stimulation. (See Fig. 16.)

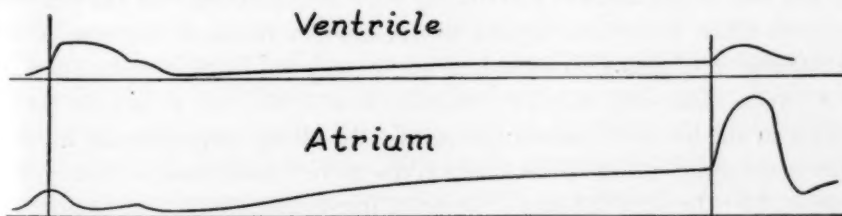


Fig. 16.—Experiment 15b. Pressure curve of atrium and ventricle during vagal stimulation. Continuous elevation of filling pressure (with Valve I).

Furthermore, it seems to me that there are a few additional basic objections to the acceptance of an optimum. It is appropriate to consider the question more precisely. In order to clarify the problem, one can consider how the skeletal muscle behaves under similar conditions.

*The following analysis applies to Dreser's paper.

If the support screw is lowered, in the case of skeletal muscle which is supported during contraction from its natural (unstretched), or greater, length, so that the initial length increases more and more (and with it the tension), the strength of contraction increases until the muscle is working without support. The weight hangs free on the muscle during contraction which has thus become purely isometric. Translating this into the language of contraction of cardiac muscle in the artificial circulation, it goes as follows: if initial tension (or filling) is continuously increased by means of raising the blood-reservoir, the ejected volume increases until the initial tension has become equal to the pressure in the arterial system. This occurs in many cases (such as Experiment 26) in which the ejected volume increases until initial tension (11.3 mm. Hg) has at least approximately reached the pressure in the arterial system (ca. 12 mm. Hg). Whether the ejected volume during extreme after-loading also increases until the contraction has become isotonic is not known.

Experiment 26:

Initial tension (mm. Hg)	2.9	3.2	3.7	4.8	5.0	6.3
Ejected volume (c.c.)	0.07	0.08	0.10	0.16	0.22	0.31
Tension	7.6	8.4	9.4	11.3		
Stroke volume	0.38	0.45	0.49	0.52		

This shows that the ejected volumes increase more rapidly at the outset, then more slowly as initial tension rises. The significance of this relationship will not be considered at this point. If the peak contractions with different after-load contractions were always equal, it is apparent that the curve representing this relationship would also represent the distensibility curve of the resting muscle. But since the peaks increase with decreasing initial tension, as has been shown to be the case, a discussion of the curve requires quantitative determination of this relation.

Thus, an *optimum* does not exist. If the blood-reservoir were raised above the level of the arterial pressure, a situation would arise which has not yet been investigated in skeletal muscle, and which, perhaps, is not realistic. Blood would, in fact, flow out of the outlet tube during ventricular relaxation [as well as during contraction], since the aortic valves would always be open because of the high initial tension. The situation would, in any case, be of little investigative interest.

It is often observed that an *optimum* is reached before initial tension and the tension in the arterial system are equal. In all my experiments in which this situation arose, the atrioventricular valves were insufficient. For example, in Experiment 15b the insufficiency manifests itself most clearly in the atrial curve. Lack of attention to this possibility may have been the source of many an erroneous determination.

Another question is whether the heart ejects larger volumes when initial tension is kept equal to arterial pressure (beginning at zero), with isotonic conditions prevailing during contraction. In accord with observations on skeletal muscle,^{20,21,22} one might guess that with lesser tensions a small increase in volume takes place. Then, as the ejected volume begins to decrease again [having passed its peak], a certain *optimum* is seen. (See Fig. 17.)

This question can only be settled by observation of the purely isotonic curve under various loads. The issue obviously cannot be decided by Dreser's experiment,⁶ in which the level of the inflow vessel and of the outlet were altered at the same time. One cannot see with certainty, from his paper, whether Dreser had in mind a solution to this particular problem. The tensions affecting the heart are not at all equal during a contraction, even when outlet opening and blood-reservoir are placed at the same level. Initial tension is, according to our argument, considerably lower than the hydrostatic pressure of the filling fluid, and tension during contraction is higher than the hydrostatic pressure in the arterial system. If both levels are raised, thus producing a rise in initial tension, the ejected volumes are increased, the increase being relatively marked at lower tensions. The rise of tension during contraction (increase in after-load) causes a decrease in the amount of ejected blood, as will be seen later. At the outset, the size of the decrease is less than that of the increase associated with higher initial tension. Therefore, an ejection maximum must result, the underlying causes of which are complicated and uncontrollable. This maximum has, of course, nothing to do with the maximum in question.

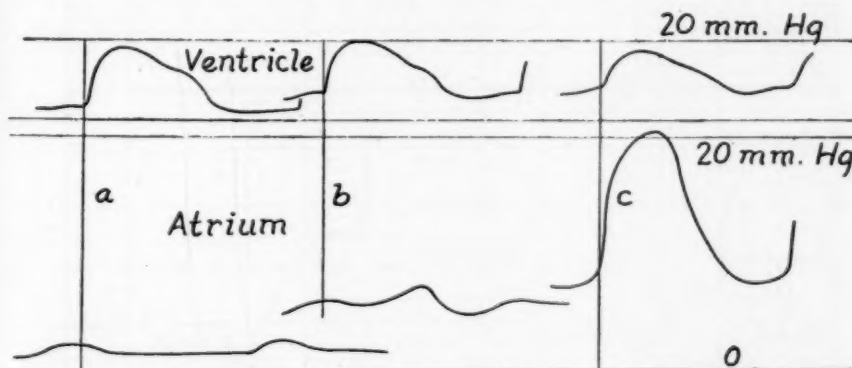


Fig. 17.—Experiment 15b. Apparent optimum with rising filling pressure at *b*; effect of insufficiency shown at *c*.

From the preceding discussion it seems that the effect of any agent, whether toxin or nerve stimulation, on the amount of shortening of cardiac muscle must be determined either by observation of the level of contraction under isotonic conditions with constant loads—and this should be the method first to be applied—or by holding initial tension absolutely constant during an experiment. The latter can be achieved rather well by omitting Valve I. If this is done, the actual initial tension is approximately equal to the hydrostatic pressure, provided the natural atrioventricular valve offers only minor resistance, as is probably the case. This procedure cannot be used, of course, in Dreser's method, in which two valves are indispensable.

How, then, are the pressure curves in the various parts of the circulatory apparatus altered with increase of initial tension? (See Figs. 17, 18, and 19.) Starting from the lowest initial tensions, we see the initial part of the ventricular pressure curve, occurring during the strain [isometric contraction] phase, growing

steeper (and the beginning of ejection earlier). With the highest initial tension the steepness of the initial portion of the ventricular pressure curve begins to fall off again. Since this curve segment runs isometrically, we need only recall the changes of the isometric curve with initial tension in order to understand these phenomena.



Fig. 18.—Experiment 26. Pressure curves of ventricle and artery with rising filling pressure.

During ejection, as determined from the ventricular pressure curve, the low level of the maximum with low initial tensions is quite striking. It indicates low velocity during [myocardial] shortening and becomes understandable if we consider that by decrease of initial tension or diminution of the *Ausgangshöhen*

an increasingly late segment of the shortening curve is isolated. In these late segments, the velocity of shortening has already become very small. The adjoining diagram may explain this (Fig. 20).

With increase in filling, velocity also increases, especially in the last part of the ejection period, lasting longer and longer and falling off later and later.

Closure of the aortic valves is retarded with increasing filling. This indicates, according to the previous discussion, a retardation of the apex of the curve of shortening. If this should be verified, a fact established by von Kries¹² for skeletal muscle would be proved for cardiac muscle. Von Kries has indeed demonstrated that the peak time for the after-load contraction is shortened by raising the support screw, the latter corresponding to a decrease in initial tension.

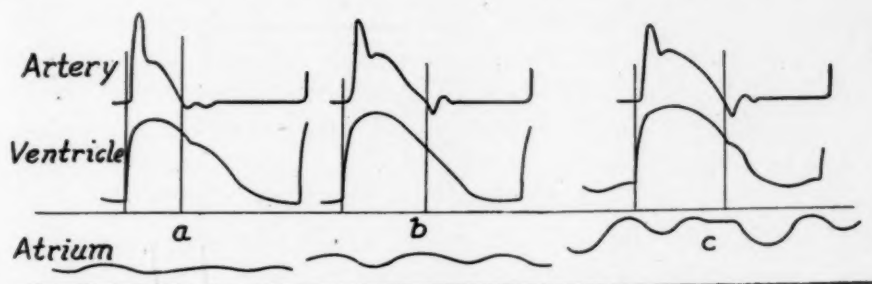


Fig. 19.—Experiment 17c. Pressure curves of atrium, ventricle, and artery with increasing filling pressure.

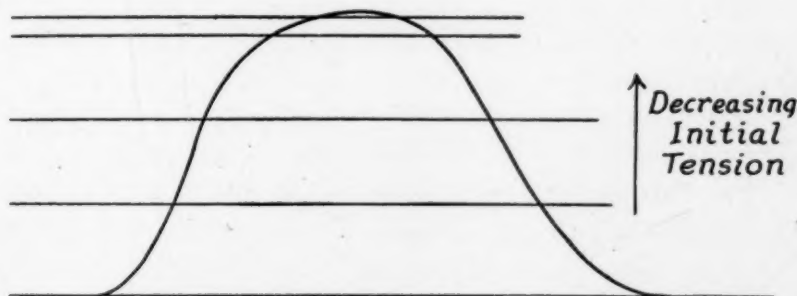


Fig. 20.—Diagram of after-load contractions.

Deduction of the principle that in cardiac muscle the maximum of the isotonic curve also occurs later than the maximum of the isometric curve is based on the fact that in the after-load contraction, aortic valve closure or maximal shortening occurs after the maximum of the isometric curve. This conclusion is all the more valid because the peak time in the after-load method is shortened in comparison with the peak time of the purely isotonic curve.

The notch indicating closure of the aortic valves is much less pronounced at low [than at high] initial tensions. This would mean that after the peak the shortening curve declines considerably slower with low initial tensions. Under the same conditions the curve rises slower before the peak. This is based on the observation that the velocity curve (see arterial curves in Figs. 18 and 19) de-

clines rapidly from its maximum and returns approximately to its base line. At higher initial tensions, velocity is sustained longer. Thus the significant phenomenon that valve closure at lower initial tensions causes a smaller notch in the arterial curve than at higher initial tensions may be ascribed to the following: the change of velocity of shortening at the time of the peak of the shortening curve (the instant at which velocity changes from positive to negative) takes place much more rapidly at higher initial tensions than at lower ones.

Von Kries' curves are not suitable for studying the above-mentioned phenomena since they do not allow exact measurement of velocity. They should be examined in skeletal muscle in more detail. They may depend on the fact that the ejection period is not completely isotonic.

Premature closure of the aortic valve causes longer duration of tension in the ventricle after closure, and with it, retardation of blood flow from atrium to ventricle (Fig. 19). According to the investigations of von Kries,¹² one would also anticipate that the peak of the after-load contraction would become higher with increasing support (lower initial tension).

I believe that a phenomenon which can be observed in the heart must be considered in this connection. If inflow is cut off by closing Stopcock I (Fig. 1), the heart never empties in one beat, but only after two or three beats, even if the level of the outflow tube is unchanged so that tension during contraction remains approximately the same. This proves that the heart does not usually empty completely, that there is always some residual volume, and that with smaller fillings it contracts to a smaller volume than with larger ones. Thus the analogy with the skeletal muscle is in this way established and the applicability of von Kries' principle to heart muscle becomes entirely probable.

Raising initial tension causes the notch of valve closure to fall lower on the descending limb of the ventricular pressure curve. This is the extent to which one can go concerning changes in ventricular and arterial pressure curves.

Mean pressure rises, of course, in the atrial curve, and, in the method employing Valve I, the first curve peak (signalling the opening of the atrioventricular valve) rises above the second one, which is produced by atrial contraction (Fig. 17, *a* and *b*).

The relationship between tension at the beginning of ventricular contraction and filling poses an interesting problem. From my experiments it can be seen that tension rises as filling increases, and that it would furnish a measure of filling if one knew the distensibility curve of resting heart muscle.* The determination of this relation would be helpful in connection with many problems of cardiac filling, which itself cannot be measured directly. Initial tension could be used to deduce the volume of the heart in relaxation. As already mentioned, the relationship cannot be determined from my observations.

(To be continued in the September issue.)

*Dreser⁶ determined such a curve.

REFERENCES

1. Gaskell, W. H.: On the Rhythm of the Heart of the Frog, and on the Nature of the Action of the Vagus Nerve, *Proc. Roy. Soc. London* **33**:199-203, 1881-2.
2. Engelmann, T. W.: Beobachtungen und Versuche am suspendirten Herzen, *Arch. ges. Physiol.* **52**:357-393, 1892.
3. Marey, E.-J.: La circulation du sang à l'état physiologique et dans les maladies, Paris, 1881, G. Masson.
4. Blasius, W.: Am Froschherzen angestellte Versuche über die Herz-Arbeit unter verschiedenen innerhalb des Kreislaufes herrschenden Druck-verhältnissen, *Physikalische Medizin Gesellschaft zu Würzburg. Verhandlungen (neue Folge)* **2**:49-89, 1872.
5. Williams, F.: Über die Ursache der Blutdrucksteigerung bei der Digitalinwirkung, *Arch. f. exper. Path. u. Pharmacol.* **13**:1-13, 1880.
6. Dreser, H.: Über Herzarbeit und Herzgifte, *Arch. f. exper. Path. u. Pharmacol.* **24**:221-240, 1887.
7. Hürthle, K.: Orientirungsversuche über die Wirkung des Oxyspartein auf das Herz, *Arch. f. exper. Path. u. Pharmacol.* **30**:141-156, 1892.
8. Frank, O.: Die Vervielfältigung von Curven auf photomechanischen Wege, *Arch. f. Anat. u. Physiol. (Du Bois-Reymond)*, *Physiologische Abteilungen*, 128-129, 1894.
9. Fick, A.: Über die Wärmeentwicklung bei der Muskelzuckung, *Pflügers Arch. Physiol.* **16**:59-90, 1878.
10. Hermann, L.: Allgemeine Muskelphysik. Handbuch der Physiologie, Edited by L. Hermann, Leipzig, 1879-1882, Vogel, Vol. 1, Part 1, pages 1-260 (1879).
11. Flatow, R.: Über den Einfluss der Temperatur auf die Thätigkeit des Froschherzens, *Arch. f. exper. Path. u. Pharmacol.* **30**:363-384, 1892.
12. Kries, J. v.: Untersuchungen zur Mechanik des quergestreiften Muskels, *Arch. f. Anat. u. Physiol. (Du Bois-Reymond)* *Physiologische Abteilungen*, 348-374, 1880.
13. Roether, O.: Übersichtliche Darstellung der Untersuchungsmethoden und der Giftwirkungen am Herzmuskel des Kaltbluters, Leipzig, 1891, W. Wegand.
14. Luderitz, C.: Versuche über den Ablauf des Blutdruckes bei Aortenstenose, *Ztschr. klin. Med.* **20**:374-396, 1892.
15. Blix, M.: Die Länge und die Spannung des Muskels. Erste Abhandlung, *Skandinav. Arch. Physiol.*, Leipzig **3**:295-318, 1891.* Zweite Abhandlung, *Skandinav. Arch. Physiol.*, Leipzig **4**:399-409, 1893. Dritte Abhandlung, *Skandinav. Arch. Physiol.*, Leipzig **5**:150-172, 1895. Vierte Abhandlung, *Skandinav. Arch. Physiol.*, Leipzig **5**:173-206, 1895.
16. Fick, A.: Über die Aenderung der Elasticität des Muskels während der Zuckung, *Arch. ges. Physiol.* **4**:301-315, 1871.
17. Jacobson, H.: Beiträge zur Haemodynamik, *Arch. f. Anat. u. Physiol. (Du Bois-Reymond)*, 80-113, 1860.
18. Helmholtz, H.: Vorläufiger Bericht über die Fortpflanzungsgeschwindigkeit der Nervenreizung, *Arch. f. Anat., Physiol., u. wissensch. Med. (Müller's Archiv)* **71**-73; 276-364, 1850.
19. Fick, A.: Über den Dikrotismus des Pulses, *Pflüger's Arch. Physiol.* **49**:105-110, 1891.
20. Heidenhain, R.: Mechanische Leistung, Wärmeentwicklung und Stoffumsatz bei der Muskelthätigkeit, Leipzig, 1864, Breitkopf u. Hartel.
21. Fick, A.: Untersuchungen über Muskel Arbeit, Basel, 1867.
22. Fick, A.: Beiträge zur vergleichenden Physiologie der imtablen Substanzen, Braunschweig, 1863, F. Vieweg u. Sohn.
23. Kries, J. v.: Untersuchungen zur Mechanik des quergestreiften Muskels, *Arch. f. Physiol. (Leipzig)*, 1-21, 1892.
24. Johansson, J. E., and Tigerstedt, R.: Über die gegenseitigen Beziehungen des Herzens und der Gefässe, *Skandinav. Arch. Physiol.* **1**:331-402, 1889.
25. Johansson, J. E., and Tigerstedt, R.: Über die gegenseitigen Beziehungen des Herzens und der Gefässe, Zweite Abhandlung, *Skandinav. Arch. Physiol.* **2**:409-437, 1891.
26. Roy, C., and Adami, J.: Remarks on Failure of the Heart From Overstrain, *Brit. M. J.* **2**:1321-1326, 1888.

*[The erste Abteilung is the article quoted by Frank.]

Announcements

A SEMINAR ON THE ELECTROCARDIOGRAPHIC EXERCISE TEST will be held at the DeGoesbriand Memorial Hospital, a teaching hospital of the University of Vermont College of Medicine, Burlington, Vt., on Sept. 19 and 20, 1959.

Guest speakers will include Dr. E. Donoso, New York City; Dr. H. K. Hellerstein, Cleveland, Ohio; Dr. A. M. Master, New York City; Dr. T. W. Mattingly, Washington, D.C.; Dr. G. P. Robb, New York City; Dr. H. I. Russek, New York City; and Dr. D. Scherf, New York City. There will be a \$10.00 registration fee for nonresidents of Vermont.

Inquiries should be directed to Eugene Lepeschkin, M.D., Associate Professor of Experimental Medicine, University of Vermont College of Medicine, Burlington, Vt.

THE FOURTH CONGRESS OF THE ISRAEL HEART SOCIETY will be held in Haifa, on Oct. 21-22, 1959. The main topics will be Hypertension and Atherosclerosis. There will also be free communications on clinical and experimental researches.

The Society will welcome cardiologists from abroad at the Congress. Additional information may be obtained from Dr. S. Wester, Secretary, Rothschild Hospital, 4 Wedgewood Avenue, Haifa, Israel.

THE VI INTERAMERICAN CONGRESS OF CARDIOLOGY, under the auspices of the Interamerican and Brazilian Societies of Cardiology will be held from Aug. 14 to 20, 1960, in Rio de Janeiro, Brazil. Prof. E. Magalhães Gomes is President of the Congress.

All correspondence should be addressed to the Secretary, H. Alquéres, Caixa Postal 1594, Rio de Janeiro, Brazil.

THE EIGHTH INTERIM MEETING OF THE AMERICAN COLLEGE OF CARDIOLOGY will be held at the Benjamin Franklin Hotel, Philadelphia, Pa., on Oct. 23-25, 1959, according to an announcement by Gabriel F. Greco, M.D., Ozone Park, N. Y., member of the Publication Committee.

This year for the first time the scientific sessions of the College will be concurrent with the THIRTY-SECOND ANNUAL MEETING OF THE AMERICAN HEART ASSOCIATION and will include a joint program.

The College will conduct fireside conferences on the evening of October 23, in which members of the American Heart Association will participate jointly. On October 25, a panel on Cardiac Resuscitation will be presented jointly by the College and the Association's Council on Clinical Cardiology.

The program may be obtained from Philip Reichert, M.D., Executive Director, American College of Cardiology, Empire State Bldg., New York, N. Y.

THE UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE will offer the first of a ten-course series of postgraduate programs on Sept. 28, 29, and 30, 1959. Dr. Enrique Cabrera, of the Institute of Cardiology, Mexico City, will team with Dr. Eugene Lepeschkin, of the University of Vermont, to present the three-day course in ADVANCED ELECTROCARDIOLOGY.

The fee for the course will be \$50.00. Application should be made to: Office of Medical Extension, University of Nebraska College of Medicine, 42nd and Dewey Streets, Omaha 5, Neb.